Annexe 3

COMP Report to the European Commission in Relation to Article 10 of Regulation 141/2000 on Orphan Medicinal Products

European Medicines Agency

EMEA/H/C/370

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

FABRAZYME

International Nonproprietary Name (INN): **agalsidase beta**

Abstract

Active substance:	Agalsidase beta (recombinant human a-galactosidase A)
Pharmaco-therapeutic group	Other alimentary tract and metabolism products - Enzymes.
(ATC Code):	A16AB04 agalsidase beta (pending)
Currently approved therapeutic indication(s):	For use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency).
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands
Date of issue of Marketing Authorisation valid throughout the European Union:	3 August 2001
Orphan medicinal product designation date:	8 August 2000

The active substance of Fabrazyme is agalsidase beta, a recombinant human α-galactosidase A produced by genetically engineered Chinese Hamster Ovary (CHO) cells. In patients with Fabry disease, due to lack of functioning α-galactosidase A, there is an abnormal accumulation and tissue deposition of the glyosphingolipid ceramide trihexoside (CTH) in especially the kidney, heart and nervous system and it is therefore necessary to provide these patients with a substitute of α-galactosidase A.

The approved indication is: long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency).

Clinical trials investigated the safety and efficacy of multiple intravenous doses of agalsidase beta in patients with confirmed Fabry Disease. These studies showed that Fabrazyme was adequate in terms of efficacy and safety in the treatment of these patients.

The benefits with Fabrazyme in this glycosphingolipid storage disorder include the reduction or clearance of glycosphingolipids in the plasma and cells of kidney, heart and skin. Renal function remained stable and a stabilisation of neuropathic pain was observed with treatment up to one year. These results are suggestive of a clinical improvement or a stabilisation of the clinical condition. However, the number of patients treated is relatively small and the treatment duration in the clinical trials relatively short compared to the long-term treatment necessary for Fabry Disease.

The most common side effects are hypersensitivity reactions, which were manageable with appropriate interventions.

The CHMP, on the basis of quality, efficacy and safety data submitted, considered that the benefit risk ratio for Fabrazyme is favourable in the approved indication.
The CHMP recommended that the Marketing Authorisation should be granted under exceptional circumstances because the indication for which the product in question is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence under normal conditions of use. Due to the evidence provided to support the rationale for a beneficial effect of enzyme replacement therapy, it is considered acceptable that the Marketing Authorisation Holder will submit additional clinical data as post-marketing obligations. These long-term safety and efficacy data shall form the basis of the annual reassessment of the benefit/risk profile for Fabrazyme. In addition, the Marketing Authorisation Holder will submit additional information on chemical, pharmaceutical and biological aspects of this medicinal product.

All additional studies will be carefully monitored and the results will be reviewed by the CHMP.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

REPLAGAL

International Nonproprietary Name (INN): **Agalsidase alfa**

Abstract

Active substance:	Agalsidase alfa
Pharmaco-therapeutic group (ATC Code):	Other alimentary tract and metabolism products – Enzymes A16AB03 agalsidase alfa
Currently approved therapeutic indication:	For use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency).
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	TKT Europe AB Rinkebyvägen 11B SE 182 36 Danderyd Sweden
Date of issue of Marketing Authorisation valid throughout the European Union:	3 August 2001
Orphan medicinal product designation date:	8 August 2000

The active substance of Replagal, agalsidase alfa, is a human α-galactosidase A produced by genetic engineering technology in a human cell line. In patients with Fabry disease, due to lack of functioning α-galactosidase A, there is an abnormal accumulation and tissue deposition of the glyosphingolipid ceramide trihexoside (CTH) in especially the kidney, heart and nervous system and it is therefore necessary to provide these patients with a substitute of α-galactosidase A.

The approved indication is: long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency).

Clinical trials investigated the safety and efficacy of multiple intravenous doses of agalsidase alfa in male patients with confirmed Fabry Disease. These studies showed that Replagal was adequate in terms of efficacy and safety in the treatment of these patients. The benefits with Replagal in this glycosphingolipid storage disorder include the reduction of neuropathic pain, initial stabilisation followed by improvement of renal function with long-term use and a reduction of cardiac mass. A reduction of glycosphingolipid content in the plasma, urine sediment and cells of kidney, heart and liver was also observed. These results are suggestive of an improvement of the clinical condition with continued Replagal therapy. However, the number of patients treated is relatively small and the treatment duration in the clinical trials relatively short compared to the long-term treatment necessary for Fabry Disease.

The most common side effects are infusion reactions, which were manageable with appropriate interventions. The CHMP, on the basis of quality, efficacy and safety data submitted, considered that the benefit risk ratio for Replagal is favourable in the approved indication.

The CHMP recommended that the Marketing Authorization should be granted "under exceptional circumstances because the indication for which the product in question is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence under normal conditions of use. Due to the evidence provided to support the rationale for a beneficial effect of enzyme replacement therapy, it is considered acceptable that the Marketing Authorisation Holder will submit additional clinical data as post-marketing obligations. These long-term safety and efficacy data shall form the basis of the annual reassessment of the benefit/risk profile for Replagal. In addition, the Marketing Authorization Holder will submit additional information on chemical, pharmaceutical and biological aspects of this medicinal product.

All additional studies will be carefully monitored and the results will be reviewed by the CHMP.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

TRISENOX

International Nonproprietary Name (INN): **Arsenic trioxide**

Abstract

Active substance:	Arsenic trioxide
Pharmacotherapeutic group (ATC Code):	Other antineoplastic agents (L01XX27)
Currently approved therapeutic indication(s):	TRISENOX is indicated for induction of remission and consolidation in adult patients with relapsed/refractory acute promyelocytic leukaemia (APL), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene. Previous treatment should have included a retinoid and chemotherapy. The response rate of other acute myelogenous leukaemia subtypes to TRISENOX has not been examined.
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Cell Therapeutics UK Limited 100 Pall Mall London SW1Y 5HP United Kingdom
Date of issue of Marketing Authorisation valid throughout the European Union:	5 March 2002
Orphan medicinal product designation date:	18 October 2000

The active substance of TRISENOX, an antineoplastic agent, has shown apoptogenic and cyto-differentiating action on acute promyelocytic leukaemia cells. The approved indication is: "TRISENOX is indicated for induction of remission and consolidation in adult patients with relapsed/refactory acute promyelocytic leukaemia (APL), characertised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid Receptor-alpha (PML/RAR-alpha) gene. Previous treatment should have included a retinoid and chemotherapy. The response rate of other acute myelogenous leukaemia subtypes to TRISENOX has not been examined".

The main clinical efficacy data submitted consisted of two non-randomised studies, which recruited a total of 52 patients with APL who had relapsed after retinoid and anthracycline chemotherapy, or for who anthracycline-based chemotherapy was contraindicated. These studies showed that overall, 45/52

(87%) patients achieved a clinical complete remission. The median time to complete remission was 57 days. At the time of last follow-up (July 28, 2000), 24 of 45 (55%) patients with complete remission remained free of disease. Thirty-one of 45 (69%) patients with complete remission were alive at last contact with median follow-up of 18.5 months (range 11.7 to 32.4). The most common adverse events observed during treatment were hyperglycaemia, hypokalaemia, neutropenia and increased alanine amino transferase. Serious adverse events were common (1-10%) in the clinical trials. Those related to TRISENOX included APL differentiation syndrome, leukocytosis, prolonged QT interval (with torsade de pointes in one case), atrial fibrillation/atrial flutter, hyperglycaemia and a variety of SAEs related to haemorrhage, infections, pain, diarrhoea, nausea.

The CHMP recommended that the Marketing Authorisation should be granted "under exceptional circumstances" because of the rarity of the indication. The Marketing Authorisation Holder will submit additional information, including randomised clinical trials to further define therapeutic strategy with TRISENOX. All additional studies will be carefully monitored and the results will be reviewed by the CHMP.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

TRACLEER

International Nonproprietary Name (INN): **Bosentan**

Abstract

Active substance:	Bosentan
Pharmaco-therapeutic group	Cardiovascular system - Antihypertensives - Other antihypertensives
(ATC Code):	C02KX01
Currently approved therapeutic indication(s):	Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with grade III functional status. Efficacy has been shown in Primary PAH and in PAH secondary to scleroderma without significant interstitial pulmonary disease.
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Actelion Registration Ltd. BSI Building 13th Floor 389 Chiswick High Road London W4 4AL United Kingdom
Date of issue of Marketing Authorisation valid throughout the European Union:	15 May 2002
Orphan medicinal product designation date:	14 February 2001

Tracleer is an endothelin receptor antagonist which decreases pulmonary vascular resistance *developed* for symptomatic treatment of pulmonary arterial hypertension Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH.

The approval was based on the results of clinical trials investigating the effects of bosentan on change in walking distance in grade III functional status patients with primary PAH or PAH secondary to scleroderma without significant interstitial pulmonary disease. The study products were added to the patient's existing PAH therapy, but patients treated with intravenous prostacycline within 3 months were not included. These studies showed that Tracleer provides a significant improvement in exercise capacity and symptoms in these patients.

The most common side effects are abnormal hepatic function, anaemia, headache, and flushing and leg oedema. Taking into account safety risks with respect to hepatotoxicity, teratogenicity, medicinal products interactions and decrease in haemoglobin, appropriate precautions and monitoring are necessary. Tracleer can also case in rare cases hypersensitivity reactions including anaphylaxis.

The CHMP, on the basis of quality, safety and efficacy data submitted, considers that the benefit risk ratio for Tracleer is favourable in the approved indication. The Marketing Authorisation was initially

granted under exceptional circumstances due to the limited clinical data available. Following the evaluation of the data submitted post-authorisation, as part of the fulfilment of specific obligations, there are no grounds for maintaining the Marketing Authorisation under exceptional circumstances.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

GLIVEC

International Nonproprietary Name (INN): **Imatinib mesilate**

Abstract

Active substance:	Imatinib mesilate
Pharmaco-therapeutic group (ATC Code):	Other antineoplastic agents (L01XX28)
Currently approved therapeutic indication:	Glivec is indicated for the treatment of patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment. Glivec is also indicated for the treatment of patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis. The effect of Glivec on the outcome of bone marrow transplantation has not been determined. Glivec is also indicated for the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST). In adult patients, the effectiveness of Glivec is based on overall haematological and cytogenetic response rates and progression-free survival in CML and objective response rates in GIST. The experience with Glivec in children with CML is very limited. There are no controlled trials demonstrating a clinical benefit or increased survival for either of the two diseases.
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Novartis Europharm Ltd Wimblehurst Road Horsham West Sussex RH12 5AB UK
Date of issue of Marketing Authorisation valid throughout the European Union:	7 November 2001
Orphan medicinal product designation date:	14 February 2001 (CML indication) 20 November 2001 (GIST indication)

The originally approved indication of Glivec is for the treatment of adult patients with Philadelphia chromosome (bcr-abl) positive chronic myeloid leukaemia (CML) in chronic phase after failure of

interferon- alpha therapy, or in accelerated phase or blast crisis. The indication was extended to patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment (including paediatric patients).. An additional indication for the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) was approved.
The active substance of Glivec is imatinib mesilate, a protein-tyrosine kinase inhibitor. Imatinib inhibits the BCR-ABL tyrosine kinase, which is crucial for the development of CML. Imatinib also inhibits the c-Kit receptor tyrosine kinases, which mediate the growth of gastrointestinal stromal tumour (GIST) cells expressing an activating *kit* mutation.

The main clinical efficacy data submitted for the originally approved indication of CML were from three open-label non-randomised phase II studies which recruited a total of 1027 patients in advanced stages of CML or in chronic phase after failure of IFN therapy. The assessment of the efficacy of Glivec was based on overall haematologic and cytogenetic response rates. There were no data from controlled trials demonstrating a clinical benefit or increased survival. Mature data on progression-free survival and overall survival for the main clinical efficacy data submitted were not yet available.

A phase III study compared treatment with either single-agent Glivec or a combination of interferon-alfa (IFN) plus cytarabine (Ara-C) in a total of 1106 newly diagnosed patients. The estimated rate of patients free of progression to accelerated phase or blast crisis at 12 months was significantly higher in the Glivec arm compared to the IFN-AraC arm. The estimated rate of progression-free survival at 12 months is 97.2% in the Glivec arm and 80.3% in the control arm. The rates of complete haematological response and major cytogenetic response were significantly higher in the Glivec arm.

A total of 26 paediatric patients of median age 12 years (range 3 to 17) with either chronic phase CML or CML in blast crisis or Ph+ acute leukaemias have been enrolled in a dose-escalation phase I trial. Out of 9 patients with chronic phase CML, 4 (44%) and 3 (33%) achieved a complete and partial cytogenetic response, respectively. Eight additional children (3 CML, 4 acute leukaemias) have been treated in another phase I study. Two out of the three chronic phase CML patients achieved a complete cytogenetic response.

A phase II, open-label, randomised, uncontrolled multinational study was conducted in 147 patients with unresectable or metastatic malignant gastrointestinal stromal tumours (GIST). The primary evidence of efficacy was based on objective response rates. Partial responses were observed in 40% of the patients and 41% of the patients achieved disease stabilization.
The most frequent adverse events observed during treatment were mild nausea, vomiting, diarrhoea, myalgia, muscle cramps, superficial oedemas as well as neutropenia and thrombocytopenia. Among the total of 34 paediatric patients, there were no special safety findings in comparison with adult trials. Intra-tumoural haemorrhages were reported in GIST patients.

Given the outstanding activity observed and in view of the applicant's commitment to complete the identified programme of studies laid out as specific obligations, the results of which shall form the basis of an annual reassessment of the benefit/risk profile, the CHMP considered that an approval under exceptional circumstances could be recommended.

The CHMP recommended that the Marketing Authorisation should be granted "under exceptional circumstances" because the indications for which the medicinal product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the quality, safety and efficacy of the medicinal product. The Marketing Authorisation Holder will submit additional information on clinical aspects of this medicinal product. All additional studies will be carefully monitored and the results will be reviewed by the CHMP.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

SOMAVERT

International Nonproprietary Name (INN): **pegvisomant**

Abstract

Active substance:	Pegvisomant
Pharmaco-therapeutic group (ATC Code):	Somatropin antagonists H01AX01
Currently approved therapeutic indication:	Treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-I concentrations or was not tolerated.
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Pfizer Limited Sandwich, Kent CT13 9NJ, United Kingdom
Date of issue of Marketing Authorisation valid throughout the European Union:	13 November 2002
Orphan medicinal product designation date:	14 February 2001

SOMAVERT is an analogue of human growth hormone that has been genetically modified to be a growth hormone receptor antagonist. Pegvisomant binds to growth hormone receptors on cell surfaces, where it blocks growth hormone binding, and thus interferes with intracellular growth hormone signal transduction. Inhibition of growth hormone action with pegvisomant leads to decreased serum concentrations of insulin-like growth factor-I (IGF-I), as well as other growth hormone-responsive serum proteins such as free IGF-I, the acid-labile subunit of IGF-I (ALS), and insulin-like growth factor binding protein-3 (IGFBP-3). Treatment should be initiated under the supervision of a physician experienced in the treatment of acromegaly.

Clinical trials investigated the efficacy of SOMAVERT in acromegalic patients (n=112) treated in a 12-week, randomised, double-blind, multicentre study comparing placebo and pegvisomant. Dose-dependent, statistically significant reductions in mean IGF-I ($p<0.0001$), free IGF-I ($p<0.05$), IGFBP-3 ($p<0.05$) and ALS ($p<0.05$) were observed at all post-baseline visits in the pegvisomant treatment groups. The serum IGF-1 was normalised at the end of the study (week 12) in 9.7%, 38.5%, 75% and 82% of subjects treated with placebo, 10 mg/day, 15 mg/day or 20 mg/day respectively. Statistically significant differences from placebo ($p<0.05$) were observed for improvements in the total signs and symptoms score for all dose groups compared to placebo.
The most frequent adverse events observed during treatment were injection site reactions, sweating, headache and asthenia. Most injection site reactions characterised as localised erythemas and soreness,

spontaneously resolved with local symptomatic treatment, while SOMAVERT therapy continued.The CHMP, on the basis of quality, efficacy and safety data submitted, considered that SOMAVERT showed adequate evidence of efficacy for the approved indications, as well as a satisfactory risk/benefit profile and therefore recommended that the Marketing Authorisation should be granted.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

ZAVESCA

International Non-proprietary Name (INN): **Miglustat**

Abstract

Active substance:	Miglustat
Pharmaco-therapeutic group (ATC Code):	Other alimentary tract & metabolism products A16AX06
Currently approved therapeutic indication(s):	Treatment of mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Actelion Registration Ltd 90 Fetter Lane (ground floor) London EC4A 7JP United Kingdom
Date of issue of Marketing Authorisation valid throughout the European Union:	20 November 2002
Orphan medicinal product designation date:	18 October 2000

Zavesca, which contains miglustat, is an alimentary tract and metabolism medicinal product. Gaucher disease is an inherited metabolic disorder caused by reduced degradation of glucosylceramide, resulting in lysosomal storage of this material and widespread pathology. *In vitro* and *in vivo* studies have shown that miglustat can reduce the synthesis of glucosylceramide through the inhibition of glucosylceramide synthase, the enzyme responsible for the first step in the synthesis of most glycolipids. This inhibitory action forms the rationale for substrate reduction therapy in Gaucher disease.

The approved indication is for oral treatment of mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable. Therapy should be directed by physicians who are knowledgeable in the management of Gaucher disease.

The pivotal clinical trial in twenty-two patients with mild to moderate type 1 Gaucher disease, who were unable or unwilling to receive enzyme replacement therapy (ERT) and who completed 12 months of treatment with Zavesca, showed a mean reduction in liver organ volume of 12.1% and a mean reduction in spleen volume of 19.0%. In addition, a mean increase in haemoglobin concentration of 0.26 g/dl as well as a mean platelet count increase of 8.29 x 10^9/l was observed. Reasons for not receiving ERT among these patients included the burden of intravenous infusions and difficulties in venous access. After 3 years of continuous Zavesca treatment, mean reductions in liver and spleen organ volume were 17.5% and 29.6%, respectively. There was a mean increase of 22.2 x

10^9/l in platelet count and a mean increase of 0.95 g/dl in haemoglobin concentration. A second open controlled study randomised 36 patients who had received a minimum of two years treatment with ERT. Patients who were switched to Zavesca over an initial 6-month period displayed small reductions in liver and spleen organ volume. However, there were reductions in platelet count and increases in chitotriosidase activity in some patients indicating that Zavesca monotherapy may not be sufficient to maintain the same control of disease activity as ERT. Although no direct comparisons with ERT have been performed in treatment naive patients, it appears that it would take longer to achieve any effect with Zavesca and there is no evidence of an efficacy or safety advantage over ERT. ERT is the standard of care for patients who require treatment for type 1 Gaucher disease. The efficacy and safety of Zavesca has not been evaluated in patients with severe Gaucher disease.
The most common side effect are gastrointestinal events and weight loss, that have been observed in more than 80% and approximately 60% of patients respectively. The majority of gastrointestinal events are mild and are expected to resolve spontaneously or after dose reduction. Approximately 30% of patients have reported tremor or exacerbation of existing tremor on treatment. Isolated cases of cognitive dysfunction have been reported. Cases of peripheral neuropathy have been reported in patients treated with Zavesca with or without concurrent conditions such as vitamin B_{12} deficiency and monoclonal gammopathy. All patients should therefore undergo baseline and repeat neurological and cognitive functions evaluations. Patients who develop symptoms should have a careful re-assessment of risk/benefit and may require cessation of treatment.

The CHMP, on the basis of quality, efficacy and safety data submitted, considered that the benefit risk profile for Zavesca is favourable in the approved indication. However, the benefit/risk profile of Zavesca was acceptable only for a small subset of patients with type 1 Gaucher disease for whom enzyme replacement therapy was unsuitable as assessed by physicians knowledgeable in the treatment of patients with this disease. This assessment forms the basis of a restricted indication.

The CHMP recommended that the Marketing Authorisation should be granted "under exceptional circumstances" since, due to the rarity of the indication, comprehensive information on the safety and efficacy of the medicinal product cannot be provided by the applicant. The Marketing Authorisation Holder will submit additional information on the safety and efficacy aspects of this medicinal product. All additional studies will be carefully monitored and the results will be reviewed by the CHMP.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

CARBAGLU

INTERNATIONAL NONPROPRIETARY NAME (INN): **CARGLUMIC ACID**

Abstract

Active substance:	Carglumic acid
Pharmaco-therapeutic group (ATC Code):	alimentary tract and metabolism product; ATC code: A16A A05
Currently approved therapeutic indication:	Treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Orphan Europe Immeuble "Le Guillaumet" F-92046 Paris La Défense France
Date of issue of Marketing Authorisation valid throughout the European Union:	24 January 2003
Orphan medicinal product designation date:	18 October 2000

The approved indication is for "the treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency". Patients with this very rare congenital urea cycle disorder cannot eliminate waste nitrogen, which accumulates in the form of ammonia; this is especially toxic for the brain and can lead, in severe cases, to reduced levels of consciousness, coma and death. For those who survive, mental retardation is a common outcome. Patients with this deficiency can present symptoms at any age (neonatal or late onset presentation).

The active substance of Carbaglu is carglumic acid (NCGA). It is a structural analogue of N-acetylglutamate, which is a necessary activator of carbamoyl phosphate synthetase, the first enzyme of the urea cycle. In patients with N-acetylglutamate synthase (NAGS) deficiency, production of N-acetylglutamate is impaired.

The clinical benefit of NCGA in NAGS deficiency has been evaluated in a retrospective series of 12 treated patients who had either a neonatal or late onset presentation of the disease and were treated for a median of 3.1 years with NCGA. The data showed that ammonia levels were normalised after introduction of treatment and patients had a normal growth and psychological development. Additional analysis on the prognosis of the disease provided insight on the effect size in terms of mortality in favour of NCGA compared to no treatment or conventional therapy, which can be considered large enough in view of the lack of uncontrolled study.

NCGA was well tolerated in 20 patients, who have been treated for a median of 3.6 years with NCGA. Cases of increased sweating and transaminases levels have been reported.

The CHMP, taking into account that NAGS deficiency is a rare disease with limited treatment options and with potentially devastating consequences, considered that, on the basis of limited data efficacy and safety data submitted, Carbaglu showed adequate evidence of efficacy for the approved indication, as well as a satisfactory risk/benefit profile and therefore recommended that the Marketing Authorisation should be granted. Considering that comprehensive data on the efficacy and safety cannot be provided under normal conditions of use because of the rarity of the disease, the CHMP recommended the granting of the Marketing Authorisation under exceptional circumstances. The Marketing Authorisation Holder will submit additional information on pre-clinical and clinical aspects. In particular the applicant will conduct a systematic follow-up of patients treated with Carbaglu to gather further information on the efficacy and safety. All additional studies will be carefully monitored and the results will be reviewed by the CHMP.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

ALDURAZYME

International Nonproprietary Name (INN): **laronidase**

Abstract

Active substance:	Laronidase
Pharmaco-therapeutic group (ATC Code):	Pharmacotherapeutic group: Alimentary tract and metabolism products - enzymes. (ATC code: A16AB05)
Currently approved therapeutic indication:	Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis I (MPS I; α-L-iduronidase deficiency) to treat the non-neurological manifestations of the disease
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Genzyme Europe B.V. Gooimeer 10 NL-1411 DD Naarden The Netherlands
Date of issue of Marketing Authorisation valid throughout the European Union:	10 June 2003
Orphan medicinal product designation date:	14 February 2001

Laronidase, is a recombinant human α-L-iduronidase produced by genetically engineered Chinese Hamster Ovary (CHO) cells. MPS I is a mucopolysaccharide storage disorder caused by the deficiency of a specific lysosomal enzyme (α-L-iduronidase) required for the catabolism of glycosaminoglycans (GAGs). The rationale for enzyme replacement therapy is to restore a level of enzymatic activity sufficient to hydrolyse the accumulated substrate and to prevent further accumulation. Aldurazyme treatment should be supervised by a physician experienced in the management of patients with MPS other or I inherited metabolic diseases.

Clinical trials investigated the safety and efficacy of multiple intravenous doses of laronidase in patients with a confirmed diagnosis of MPS I. Although patients representing the full range of the disease spectrum were enrolled, the majority of the patients were of the intermediate phenotype, with only one patient exhibiting the severe phenotype. The benefits with Aldurazyme include improvements in lung function (change in percent predicted FVC compared to placebo) and walking ability (change in 6-minute walk test compared to placebo). Normalisation of liver volume occurred in the majority of patients who had abnormal liver volumes at baseline. Further, there was a rapid reduction in the excretion of urinary GAG. To date no clinical data exist demonstrating a benefit on the neurological manifestations of the disorder.The most common adverse events observed during treatment were infusion-associated reactions (IARs), which were managable with appropriate interventions. Although the majority of the IARs were of mild intensity, consisting of flushing and

headache, some of these IARs may be severe.The CHMP, on the basis of efficacy and safety data submitted, considered that Aldurazyme showed adequate evidence of efficacy for the approved indication, as well as a satisfactory risk/benefit profile and therefore recommended that the Marketing Authorisation should be granted.
The CHMP recommended that the Marketing Authorisation should be granted "under exceptional circumstances" because the indication for which the medicinal product in question is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the safety and efficacy of the medicinal product. The Marketing Authorisation Holder will submit additional information on clinical aspects of this medicinal product. All additional studies will be carefully monitored and the results will be reviewed by the CHMP.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

BUSILVEX

International Nonproprietary Name (INN): **Busulfan**

Abstract

Active substance:	Busulfan
Pharmaco-therapeutic group (ATC Code):	Alkylating agents (L01AB01)
Currently approved therapeutic indication:	Busilvex followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option.
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Pierre Fabre Médicament 45, place Abel Gance F-92654 Boulogne Billancourt Cedex France
Date of issue of Marketing Authorisation valid throughout the European Union:	9 July 2003
Orphan medicinal product designation date:	29 December 2000

The active substance of Busilvex is busulfan, a cytotoxic agent (alkylating agent) medicinal product (L01AB01) with myeloablative properties. Busilvex followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option. Clinical trials investigated exposure to busulfan following intravenous administration of Busilvex, compared to oral busulfan. These studies have to a reasonable extent shown that the chosen intravenous dose of 0.8 mg/kg gives an exposure comparable to that with the established oral dose of 1 mg/kg.

The most frequent adverse events observed during treatment were nausea, stomatitis, vomiting, anaemia, fever, anorexia, diarrhoea and insomnia.

The CHMP, on the basis of efficacy and safety data submitted, considered that Busilvex showed adequate evidence of efficacy for the approved indication, as well as a satisfactory risk/benefit profile and therefore recommended that the Marketing Authorisation should be granted.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

VENTAVIS

INTERNATIONAL NONPROPRIETARY NAME (INN): **Iloprost**

Abstract

Active substance:	Iloprost
Pharmaco-therapeutic group (ATC Code):	Platelet aggregation inhibitiors excluding heparin (B01AC)
Currently approved therapeutic indication(s):	Treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms.
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Schering AG Müllerstraße 170 – 178 13342 Berlin Germany
Date of issue of Marketing Authorisation valid throughout the European Union:	16 September 2003
Orphan medicinal product designation date:	29 December 2000

Ventavis contains iloprost, a synthetic prostacyclin analogue *developed* for treatment of patients with NYHA functional class III primary pulmonary hypertension (PPH), to improve exercise capacity and symptoms. The inhalation of Ventavis causes direct vasodilatation of the pulmonary arterial bed with consecutive significant improvement of pulmonary arterial pressure, pulmonary vascular resistance and cardiac output, as well as mixed venous oxygen saturation. Ventavis treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary hypertension.

The initial approval was based on the results of 2 randomised clinical trials investigating the safety and efficacy of inhaled iloprost when added to patients' current therapy in patients with stable pulmonary hypertension. These studies showed that Ventavis improves exercise capacity and symptoms. A prespecified subgroup analysis of 49 patients with PPH receiving treatment with inhaled iloprost for 12 weeks showed a mean increase in the 6-minute walk test of 44.7 meters from a baseline mean value of 329 meters vs. a change of -7.4 meters from a baseline mean value of 324 meters in the placebo group (46 patients in the placebo group).

The most common side effects observed in the clinical studies were headache, jaw pain, nausea, hypotension and vasodilation. Trismus with unclear mechanism occurred as a common adverse reactions. Syncope is a common symptom of the disease itself, but can also occur under therapy.
The CHMP, on the basis of quality, safety and efficacy data submitted, considered that the benefit risk ratio for Ventavis is favourable in the approved indication. The Marketing Authorisation was granted under exceptional circumstances because the indication for which the medicinal product in question is intended is encountered so rarely that the applicant could not reasonably be expected to provide comprehensive evidence/data on the safety and efficacy of the medicinal product. For detailed

conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

- Marketing Authorisation under exceptional circumstances refers to the fact that in exceptional circumstances an authorisation may be granted subject to certain specific obligations, to be reviewed annually.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

ONSENAL

International Nonproprietary Name (INN): **Celecoxib**

Abstract

Active substance:	Celecoxib
Pharmaco-therapeutic group (ATC Code):	Antineoplastic L01XX33
Currently approved therapeutic indication(s):	Onsenal is indicated for the reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance. The effect of Onsenal-induced reduction of polyp burden on the risk of intestinal cancer has not been demonstrated.
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Pharmacia - Pfizer EEIG Hillbottom Road High Wycombe Bucks HP12 4HP United Kingdom
Date of issue of Marketing Authorisation valid throughout the European Union:	17 October 2003
Orphan medicinal product designation date:	20 November 2001

The active substance of Onsenal is celecoxib, an orally active selective inhibitor of cyclooxygenase-2 (COX-2)(ATC Code: L01XX33). Elevated levels of COX-2 are found in many pre-malignant lesions (such as adenomatous colorectal polyps in patients with FAP) and epithelial cancers. Experimental evidence shows that the mechanism(s) of action by which celecoxib leads to tumour death may be related to induction of apoptosis and inhibition of angiogenesis. Inhibition of COX-2 may have consequences on tumour viability that are unrelated to inflammation.

Clinical trials investigated the safety and efficacy of celecoxib in 83 patients with FAP. The benefits with Onsenal include the reduction of the number and size of adenomatous colorectal polyps. The mean reduction in the number of colorectal polyps following six months of treatment was 28% (SD $\pm$ 24%) for celecoxib 400 mg BID, which was statistically superior to placebo (mean 5%, SD $\pm$16%). A reduction in duodenal adenoma area was also observed compared with placebo (14.5% celecoxib 400 mg BID versus 1.4% placebo), which however was not statistically significant.

The most common adverse events observed during treatment were diarrhoea, dyspepsia, fatigue, blood per rectum (rectal spotting), upper respiratory infection and rash. The adverse event profile reported

for FAP patients was similar to that reported for arthritis patients. Intestinal anastomotic ulceration was the only new adverse event reported in the FAP trial and was observed in 3 of 58 patients who had prior intestinal surgery: these events were minor and not of clinical concern.The CPMP, on the basis of efficacy and safety data submitted, considered that Onsenal showed adequate evidence of efficacy for the approved indication, as well as a satisfactory risk/benefit profile and therefore recommended that the Marketing Authorisation should be granted.

The CPMP recommended that the Marketing Authorisation should be granted "under exceptional circumstances because the indication for which the medicinal product in question is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the safety and efficacy of the medicinal product. The Marketing Authorisation Holder will submit additional information on clinical aspects of this medicinal product. All additional studies will be carefully monitored and the results will be reviewed by the CPMP.

In July 2002, France notified the EMEA and submitted grounds for a referral under Article 31 of Council Directive 2001/83/EC as amended for medicinal products containing celecoxib, etoricoxib, rofecoxib, valdecoxib and parecoxib.

The CPMP, during its meeting held from 23 to 25 July 2002 decided to start a referral procedure under Article 31 of Directive 2001/83/EC as amended, for medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib. The questions identified related to gastrointestinal and cardiovascular safety. In October 2002, the CPMP asked additional questions relating to serious hypersensitivity reactions (anaphylaxis and angioedema) and serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and exfoliative dermatitis in patients treated with COX-2 inhibitors.

During its meeting, held from 18 to 20 November 2003, the CPMP concluded that the benefit-risk balance for these products remains positive for the target patient populations. However to promote the safe use of the products, the Committee recommends adding or strengthening warnings, in particular recommending caution for patients with underlying gastrointestinal and cardiovascular risks. The Committee also recommends adding (or modifying) warnings concerning the risk of severe skin and hypersensitivity reactions. The recommendations apply to all these substances whether authorised through the European centralised procedure or through mutual recognition procedures. Therefore, the Marketing Authorisation Holder for Onsenal was requested to submit a variation to implement the changes in the Summary of the Product Characteristics and in the Package Leaflets as requested in the conclusions of the scientific assessment. This variation was submitted in January 2004, a positive Opinion was given by the CPMP on 26 February 2004 and the Commission Decision was issued on 22 April 2004.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

PHOTOBARR

International Nonproprietary Name (INN): **Porfimer sodium**

Abstract

Active substance:	Porfimer sodium
Pharmaco-therapeutic group (ATC Code):	Photodynamic Therapy (L01X D01)
Currently approved therapeutic indication:	Ablation of high-grade dysplasia (HGD) in patients with Barrett's Oesophagus.
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Axcan Pharma International BV
Date of issue of Marketing Authorisation valid throughout the European Union:	25 March 2004
Orphan medicinal product designation date:	6 March 2002

The active substance of PhotoBarr is Porfimer sodium, a photodynamic therapy medicinal product used in the therapy of certain tumours. The product is a complex mixture of porphyrin oligomers produced from hematoporphyrin dihydrochloride. PhotoBarr produces cytotoxic oxygen radicals when activated by light at selected wavelengths in the presence of oxygen.

The approved indication is "Photodynamic therapy (PDT) with PhotoBarr is indicated for: Ablation of high-grade dysplasia (HGD) in patients with Barrett's Oesophagus (BO)".

One randomized clinical trial investigated the safety and efficacy of PhotoBarr photodynamic therapy plus omeprazole compared to omeprazole. Eligible patients for this study were to have biopsy-proven high-grade dysplasia in Barrett's Oesophagus. This study showed that PhotoBarr is the first conservative treatment of high-grade dysplasia in Barrett's Oesophagus with a documented effect on progression to cancer.

The most common side effects are photosensitivity reactions that consist mainly of sunburn-like reactions (for example, mild redness on exposed skin, usually the face and hands). Other very common side effects were tightening of the oesophagus, vomiting, fever, difficulty in swallowing, constipation, dehydration, and nausea.

The CHMP, on the basis of efficacy and safety data submitted, considered that PhotoBarr showed adequate evidence of efficacy for the approved indication, as well as a satisfactory risk/benefit profile and therefore recommended that the Marketing Authorisation should be granted.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

LITAK

International Nonproprietary Name (INN): **Cladribine**

Abstract

Active substance:	Cladribine
Pharmaco-therapeutic group (ATC Code):	Purine analogue (cytostatic drug) (L01BB04)
Currently approved therapeutic indication:	LITAK is indicated for the treatment of hairy cell leukaemia
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Lipomed GmbH Schönaugasse 11 D-79713 Bad Säckingen Germany
Date of issue of Marketing Authorisation valid throughout the European Union:	14 April 2004
Orphan medicinal product designation date:	19 September 2001

The active substance of LITAK is cladribine, a purine analogue (cytostatic medicinal product) acting as an antimetabolite. Cladribine is a prodrug that is taken up rapidly in cells and activated, particularly in lymphocytes and in other haematopoietic cells. The activated cladribine blocks the synthesis of new DNA, and blocks the DNA repair mechanisms. It also blocks an enzyme called ribonucleotide reductase, which is important for the synthesis of new DNA. Cell death occurs from energy depletion and apoptosis.

The approved indication is for treatment of hairy cell leukaemia. It is proposed that therapy with LITAK should be initiated by a qualified physician with experience in cancer chemotherapy.

Clinical trials investigated the use of LITAK administered as a subcutaneous bolus injection in patients with hairy cell leukaemia. At the recommended subcutaneous dose of 0.14 mg/kg body weight/day for 5 consecutive days, uncontrolled trials showed that LITAK had similar efficacy to what has been reported in the literature using a dose of 0.1 mg/kg/day administered by continuous intravenous infusion for 7 days.

The most common side effects are myelosuppression, especially severe neutropenia, severe thrombocytopenia and severe anaemia, as well as severe immunosuppression/lymphopenia, infections and fever.

The CHMP, on the basis of quality, efficacy and safety data submitted, considered that LITAK showed adequate evidence of efficacy for the approved indication, as well as a satisfactory risk/benefit profile and therefore recommended that the Marketing Authorisation should be granted.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

LYSODREN

International Nonproprietary Name (INN): **mitotane**

Abstract

Active substance:	Mitotane
Pharmaco-therapeutic group (ATC Code):	Enzyme inhibitors. ATC code: L02BG
Currently approved therapeutic indication:	Symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma. The effect of Lysodren on non-functional adrenal cortical carcinoma is not established.
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Laboratoire HRA Pharma 19 rue Frédérick Lemaître 75020 Paris France
Date of issue of Marketing Authorisation valid throughout the European Union:	28 April 2004
Orphan medicinal product designation date:	12 June 2002

The active substance of Lysodren is mitotane (ATC code: L02BG). The approved indication is the symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma (the effect of Lysodren on non-functional adrenal cortical carcinoma is not established).

The demonstration of the clinical benefit of mitotane was based on bibliographical data in patients with inoperable or metastatic adrenal carcinoma. Mitotane induces a state of adrenal insufficiency which leads to the disappearance of Cushing syndrome in patients with secreting adrenal carcinoma but necessitates substitution hormonotherapy. The efficacy of mitotane on overall survival is not established. Special warnings and special precautions for use concerning pregnant women and women of childbearing potential were introduced in the summary of product characteristics for Lysodren. Breast-feeding is contra-indicated while taking mitotane. Once given orally, mitotane accumulates mainly in fat tissues; the terminal half-life of mitotane is very long and was reported to range from 18 to 159 days. Side effects occur in more than 80% of the patients treated with mitotane and consist mainly of gastro-intestinal disorders (reported to occur in more than 10% of the patients) and nervous system disorders (more than 40% of the patients).

The CPMP, on the basis of efficacy and safety data submitted, considered that Lysodren showed adequate evidence of efficacy for the symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma (the effect of Lysodren on non-functional adrenal cortical

carcinoma is not established), as well as a satisfactory risk/benefit profile and therefore recommended that the Marketing Authorisation should be granted.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

PEDEA

International Nonproprietary Name (INN): **ibuprofen**

Abstract

Active substance:	Ibuprofen
Pharmaco-therapeutic group (ATC Code):	Other cardiac preparations C01 EB16
Currently approved therapeutic indication:	Treatment of a haemodynamically significant patent *ductus arteriosus* in preterm newborn infants less than 34 weeks of gestational age.
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Orphan Europe S.A.R.L. Immeuble « Le Guillaumet » F-92046 Paris La Défense, France
Date of issue of Marketing Authorisation valid throughout the European Union:	29 July 2004
Orphan medicinal product designation date:	14 February 2001

The active substance of Pedea, ibuprofen, is a non-selective inhibitor of cyclo-oxygenase, leading to reduced synthesis of prostaglandins. Since prostaglandins are involved in the persistence of the *ductus arteriosus* after birth, this effect is believed to be the main mechanism of action of ibuprofen in the treatment of a patent *ductus arteriosus* (PDA).. Treatment with Pedea should only be carried out in a neonatal intensive care unit under the supervision of an experienced neonatologist.

The approval was based on the results of clinical trials investigating the safety and efficacy of ibuprofen in patients with PDA. In a dose-response study of Pedea in 40 preterm newborn infants, the *ductus arteriosus* closure rate associated with a 10-5-5 mg/kg dose regimen was 75% (6/8) in neonates of 27-29 weeks' gestation and 33% (2/6) in neonates of 24-26 weeks' gestation.

The most frequent adverse events observed during treatment were thrombocytopenia, neutropenia, bronchopulmonary dysplasia, and increased blood creatinine- and decreased blood sodium levels.

The CHMP, on the basis of quality, efficacy and safety data submitted, considered that the benefit/risk ratio for Pedea is favourable in the approved indication.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

WILZIN

International Nonproprietary Name (INN): **zinc acetate dihydrate**

Abstract

Active substance:	Zinc acetate dihydrate
Pharmaco-therapeutic group (ATC Code):	Various alimentary tract and metabolism products A16AX05
Currently approved therapeutic indication:	Wilzin is approved for the treatment of Wilson`s disease
Authorised presentations:	See the Module ”All authorised presentations”
Marketing Authorisation Holder:	Orphan Europe SARL Immeuble "Le Guillaumet" F-92046 Paris La Défense France
Date of issue of Marketing Authorisation valid throughout the European Union:	13 October 2004
Orphan medicinal product designation date:	31 July 2001

Wilzin is approved for the treatment of Wilson’s disease. Wilzin treatment should be initiated under the supervision of a physician experienced in the treatment of Wilson’s disease.

The active substance of Wilzin is zinc acetate dihydrate, an alimentary tract and metabolism medicinal product. Zinc cation, the active moiety of zinc acetate dihydrate, blocks the intestinal absorption of copper from the diet and the reabsorption of endogenously secreted copper. It induces the production of metallothionein in the enterocyte, a protein that binds copper thereby preventing its transfer into the blood. The bound copper is then eliminated in the stool following desquamation of the intestinal cells.

Clinical trials investigated safety and efficacy of zinc acetate dihydrate in presymptomatic and symptomatic Wilson’s disease patients. These studies showed that Wilzin slowly deplete the body's excess copper thus maintaining body copper at subtoxic level in presymptomatic patients and preventing reaccumulation of copper as well as copper toxicity in symptomatic patients.

The most common adverse event observed during treatment was gastric irritation.

The CHMP, on the basis of quality, efficacy and safety data submitted, considered that WILZIN showed adequate evidence of efficacy for the approved indication, as well as a satisfactory risk/benefit profile and therefore recommended that the Marketing Authorisation should be granted.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

XAGRID

International Nonproprietary Name (INN): **anagrelide**

Abstract

Active substance:	Anagrelide hydrochloride
Pharmaco-therapeutic group (ATC Code):	Other Antineoplastic Agents (L 01 X)
Currently approved therapeutic indication:	Xagrid is indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. An at risk essential thrombocythaemia patient is defined by one or more of the following features: >60 years of age, or a platelet count >1000 x 10^9/l, or a history of thrombo-haemorrhagic events.
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Shire Pharmaceutical Contracts Limited Hampshire International Business Park Chineham, Basingstoke Hampshire, RG24 8EP United Kingdom
Date of issue of Marketing Authorisation valid throughout the European Union:	16 November 2004
Orphan medicinal product designation date:	29 December 2000

Xagrid (anagrelide) is a novel imidazoquinazoline, developed for the treatment of essential thrombocythaemia (ET), acting through inhibition of platelet formation in man mediated via retardation of maturation of megakaryocytes. Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III. Treatment with Xagrid capsules should be initiated by a clinician with experience in the management of ET.

The approval was based on the results of four open-label, non-controlled clinical trials including more than 4000 patients with myeloproliferative disorders (MPDs). The benefits with Xagrid include the reduction of elevated platelet counts. In patients with ET, complete response was defined as a decrease in platelet count to ≤600 x10^9/l or a ≥50% reduction from baseline and maintenance of the reduction for at least 4 weeks. In these studies, the time to complete response ranged from 4 to 12 weeks. Clinical benefit in terms of thrombohaemorrhagic events has not been convincingly demonstrated.

The Marketing Authorisation Holder will submit additional information on clinical aspects of this medicinal product as part of the post-approval commitments. All additional studies will be carefully monitored and the results will be reviewed by the CHMP. The most common side effects are

headache, palpitations, fluid retention, nausea and diarrhoea. These adverse drug reactions are expected based on the pharmacology of anagrelide (inhibition of phosphodiesterase III). Cases of cardiomegaly and congestive heart failure have been reported and anagrelide should be used with caution in patients of any age with known or suspected heart disease, and only if the potential benefits of therapy outweigh the potential risks. Because of its positive inotropic effects, a pre-treatment cardiovascular examination (including further investigation such as echocardiography, electrocardiogram) is recommended. Patients should be monitored during treatment for evidence of cardiovascular effects that may require further cardiovascular examination and investigation.

The CHMP, on the basis of quality, safety and efficacy data submitted, considers that the benefit risk ratio for Xagrid is favourable in the approved indication. The Marketing Authorisation was granted under exceptional circumstances because the indication for which the medicinal product in question is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the safety and efficacy of the medicinal product*.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

ORFADIN

International Nonproprietary Name (INN): **Nitisinone**

Abstract

Active substance:	Nitisinone
Pharmaco-therapeutic group (ATC Code):	Other alimentary and metabolism products A16A X04
Currently approved therapeutic indication:	Treatment of patients with confirmed diagnosis of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine
Authorised presentations:	2mg, 5mg, 10mg
Marketing Authorisation Holder:	Swedish Orphan International AB Drottninggatan 98 SE-111 60 Stockholm Sweden
Date of issue of Marketing Authorisation valid throughout the European Union:	21 February 2005
Orphan medicinal product designation date:	29 December 2000

Nitisinone is an enzymatic inhibitor of the tyrosine catabolic pathway developed for the treatment of hereditary tyrosinemia type 1 (HT-1). Nitisinone treatment should be initiated and supervised by a physician experienced in the treatment of HT-1 patients.

The approval was based mainly on the results of one uncontrolled study (the NTBC study) which is a worldwide compassionate use program open to all patients with HT-1 and coordinated in Sweden. A total of 257 patients with HT-1 were enrolled between February 1991 and March 2000. This study showed that Orfadin provided an improved outcome for patients in comparison to treatment with a diet restriction alone. This was reflected by both biochemical markers normalisation and clinical improvement: the risk for death, liver transplantation due to liver failure or porphyria crises was reduced, particularly in patients starting nitisinone before six months of age.

The most common side effects are visual disorders (reversible with a more restricted tyrosine and phenylalanine diet), thrombocytopenia, and leucopoenia.

The CHMP, on the basis of quality, safety and efficacy data submitted, considers that the benefit risk ratio for Orfadin is favourable in the approved indication. The Marketing Authorisation was granted under exceptional circumstances* due to limited non-clinical and clinical data. The applicant committed in specific obligations for providing complementary information in long term animal studies and establishing a post-marketing surveillance programme to monitor patients under treatment with nitisinone. Relevant data from this programme will be summarized and included in the Periodic

Safety Update Reports to EMEA. For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

* Marketing Authorisation under exceptional circumstances refers to the fact that in exceptional circumstances an authorisation may be granted subject to certain specific obligations, to be reviewed annually.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

PRIALT

International Nonproprietary Name (INN): **Ziconotide**

Abstract

Active substance:	Ziconotide acetate
Pharmaco-therapeutic group (ATC Code):	Analgesics N02BG (pending)
Currently approved therapeutic indication:	Treatment of severe, chronic pain in patients who require intrathecal (IT) analgesia.
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Elan Pharma International Ltd. WIL House Shannon Business Park, Shannon County Clare Ireland.
Date of issue of Marketing Authorisation valid throughout the European Union:	21 February 2005
Orphan medicinal product designation date:	9 July 2001

Prialt is an analgesic developed for the treatment of severe, chronic pain in patients who require intrathecal analgesia. Treatment with Prialt should only be undertaken by physicians experienced in intrathecal drug administration. Prialt is for intrathecal use only.

The approval was based on the results of three pivotal placebo-controlled clinical trials involving patients with severe and chronic pain requiring intrathecal analgesia. These studies showed that Prialt reduces pain as measured by improvements in Visual Analog Scale of Pain Intensity (VASPI) scores in these patients.

The most common side effects are dizziness, nausea, nystagmus, confusional state, gait abnormal, memory impairment, blurred vision, headache, asthenia, and vomiting. The administration of medicinal products by the intrathecal (IT) route carries the risk of meningitis.

The CHMP, on the basis of quality, safety and efficacy data submitted, considers that the benefit risk ratio for Prialt is favourable in the approved indication. The Marketing Authorisation was granted under exceptional circumstances due to the lack of long-term efficacy and safety data.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

- Marketing Authorisation under exceptional circumstances refers to the fact that in exceptional circumstances an authorisation may be granted subject to certain specific obligations, to be reviewed annually.