เอกสารกำกับยาภาษาอังกฤษ

1. NAME OF THE MEDICINAL PRODUCT

EPORATIO 2,000
EPORATIO 3,000
EPORATIO 5,000
EPORATIO 10,000
EPORATIO 20,000
EPORATIO 30,000

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EPORATIO 2,000 IU/0.5 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 2,000 international units (IU) (16.7 µg) epoetin theta in 0.5 ml solution for injection corresponding to 4,000 IU (33.3 µg) epoetin theta per ml.
EPORATIO 3,000 IU/0.5 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 3,000 international units (IU) (25 µg) epoetin theta in 0.5 ml solution for injection corresponding to 6,000 IU (50 µg) epoetin theta per ml.
EPORATIO 5,000 IU/0.5 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 5,000 international units (IU) (41.7 µg) epoetin theta in 0.5 ml solution for injection corresponding to 10,000 IU (83.3 µg) epoetin theta per ml.
EPORATIO 10,000 IU/1 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 10,000 international units (IU) (83.3 µg) epoetin theta in 1 ml solution for injection corresponding to 10,000 IU (83.3 µg) epoetin theta per ml.
EPORATIO 20,000 IU/1 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 20,000 international units (IU) (166.7 µg) epoetin theta in 1 ml solution for injection corresponding to 20,000 IU (166.7 µg) epoetin theta per ml.
EPORATIO 30,000 IU/1 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 30,000 international units (IU) (250 µg) epoetin theta in 1 ml solution for injection corresponding to 30,000 IU (250 µg) epoetin theta per ml.
Epoetin theta (recombinant human erythropoietin) is produced in Chinese Hamster Ovary Cells (CHO-K1) by recombinant DNA technology.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
The solution is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of symptomatic anaemia associated with chronic renal failure in adult patients.
- Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

4.2 Posology and method of administration

Epoetin theta treatment should be initiated by physicians experienced in the above-mentioned indications.
Posology
Symptomatic anaemia associated with chronic renal failure
Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary. Epoetin theta should be administered either subcutaneously or intravenously in order to increase haemoglobin level to not greater than 12 g/dl (7.45 mmol/l).

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dl (6.21 mmol/l) to 12 g/dl (7.45 mmol/l). A sustained haemoglobin level of greater than 12 g/dl (7.45 mmol/l) should be avoided; guidance for appropriate dose adjustment if haemoglobin values exceeding 12 g/dl (7.45 mmol/l) are observed are described below.

A rise in haemoglobin of greater than 2 g/dl (1.24 mmol/l) over a four week period should be avoided. If the rise in haemoglobin is greater than 2 g/dl (1.24 mmol/l) in 4 weeks or the haemoglobin value exceeds 12 g/dl (7.45 mmol/l), the dose should be reduced by 25 to 50%. It is recommended that haemoglobin be monitored every two weeks until levels have stabilised and periodically thereafter. If the haemoglobin level continues to increase, therapy should be interrupted until the haemoglobin level begins to decrease, at which point therapy should be restarted at a dose approximately 25% below the previously administered dose.

In the presence of hypertension or existing cardiovascular, cerebrovascular or peripheral vascular diseases, the increase in haemoglobin and the target haemoglobin value should be determined individually taking into account the clinical picture.

Treatment with epoetin theta is divided into two stages.

<u>Correction phase</u>

Subcutaneous administration: The initial posology is 20 IU/kg body weight 3 times per week. The dose may be increased after 4 weeks to 40 IU/kg, 3 times per week, if the increase in haemoglobin is not adequate (< 1 g/dl [0.62 mmol/l] within 4 weeks). Further increases of 25% of the previous dose may be made at monthly intervals until the individual target haemoglobin level is obtained.

Intravenous administration: The initial posology is 40 IU/kg body weight 3 times per week. The dose may be increased after 4 weeks to 80 IU/kg, 3 times per week, and by further increases of 25% of the previous dose at monthly intervals, if needed.

For both routes of administration, the maximum dose should not exceed 700 IU/kg body weight per week.

<u>Maintenance phase</u>

The dose should be adjusted as necessary to maintain the individual target haemoglobin level between 10 g/dl (6.21 mmol/l) to 12 g/dl (7.45 mmol/l), whereby a haemoglobin level of 12 g/dl (7.45 mmol/l) should not be exceeded. If a dose adjustment is required to maintain the desired haemoglobin level, it is recommended that the dose be adjusted by approximately 25%.

Subcutaneous administration: The weekly dose can be given as one injection per week or three times per week.

Intravenous administration: Patients who are stable on a three times weekly dosing regimen may be switched to twice-weekly administration.

If the frequency of administration is changed, haemoglobin level should be monitored closely and dose adjustments may be necessary.

The maximum dose should not exceed 700 IU/kg body weight per week.

If epoetin theta is substituted for another epoetin, haemoglobin level should be monitored closely and the same route of administration should be used.

Patients should be monitored closely to ensure that the lowest approved effective dose of epoetin theta is used to provide adequate control of the symptoms of anaemia whilst maintaining a haemoglobin concentration below or at 12 g/dl (7.45 mmol/l).

Caution should be exercised with escalation of epoetin theta doses in patients with chronic renal failure. In patients with a poor haemoglobin response to epoetin theta, alternative explanations for the poor response should be considered (see sections 4.4 and 5.1).

Symptomatic anaemia in cancer patients with non-myeloid malignancies receiving chemotherapy

Epoetin theta should be administered by the subcutaneous route to patients with anaemia (e.g. haemoglobin concentration ≤ 10 g/dl [6.21 mmol/l]). Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary.
Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dl (6.21 mmol/l) to 12 g/dl (7.45 mmol/l). A sustained haemoglobin level of greater than 12 g/dl (7.45 mmol/l) should be avoided; guidance for appropriate dose adjustment if haemoglobin values exceeding 12 g/dl (7.45 mmol/l) are observed are described below.
The recommended initial dose is 20,000 IU, independent of bodyweight, given once-weekly. If, after 4 weeks of therapy, the haemoglobin value has increased by at least 1 g/dl (0.62 mmol/l), the current dose should be continued. If the haemoglobin value has not increased by at least 1 g/dl (0.62 mmol/l) a doubling of the weekly dose to 40,000 IU should be considered. If, after an additional 4 weeks of therapy, the haemoglobin increase is still insufficient an increase of the weekly dose to 60,000 IU should be considered.
The maximum dose should not exceed 60,000 IU per week.
If, after 12 weeks of therapy, the haemoglobin value has not increased by at least 1 g/dl (0.62 mmol/l), response is unlikely and treatment should be discontinued.
If the rise in haemoglobin is greater than 2 g/dl (1.24 mmol/l) in 4 weeks or the haemoglobin level exceeds 12 g/dl (7.45 mmol/l), the dose should be reduced by 25 to 50%. Treatment with epoetin theta should be temporarily discontinued if haemoglobin levels exceed 13 g/dl (8.07 mmol/l). Therapy should be reinitiated at approximately 25% lower than the previous dose after haemoglobin levels fall to 12 g/dl (7.45 mmol/l) or below.
Therapy should be continued up to 4 weeks after the end of chemotherapy.
Patients should be monitored closely to ensure that the lowest approved dose of epoetin theta is used to provide adequate control of the symptoms of anaemia.
Special populations
Paediatric population
The safety and efficacy of Eporatio in children and adolescents aged up to 17 years have not yet been established. No data are available.
Method of administration
The solution can be administered subcutaneously or intravenously. Subcutaneous use is preferable in patients who are not undergoing haemodialysis, in order to avoid puncturing peripheral veins. If epoetin theta is substituted for another epoetin, the same route of administration should be used. In cancer patients with non-myeloid malignancies receiving chemotherapy epoetin theta should be administered by the subcutaneous route only.
Subcutaneous injections should be given into the abdomen, arm or thigh.
The injection sites should be rotated and the injection performed slowly to avoid discomfort at the site of injection.
For instructions on handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications
- Hypersensitivity to the active substance, other epoetins and derivatives or to any of the excipients listed in section 6.1.
- Uncontrolled hypertension.

4.4 Special warnings and precautions for use
General

Supplementary iron therapy is recommended for all patients with serum ferritin values below 100 µg/l or with transferrin saturation below 20%. To ensure effective erythropoiesis, iron status has to be evaluated for all patients prior to and during treatment.

Non-response to therapy with epoetin theta should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of epoetins and should therefore be corrected. Intercurrent infections, inflammatory or traumatic episodes, occult blood loss, haemolysis, aluminium intoxication, underlying haematological diseases or bone marrow fibrosis may also compromise the erythropoietic response. A reticulocyte count should be considered as part of the evaluation.

Pure red cell aplasia (PRCA)

If typical causes of non-response are excluded, and the patient has a sudden drop in haemoglobin associated with reticulocytopenia, an examination of anti-erythropoietin antibodies and the bone marrow for diagnosis of pure red cell aplasia should be considered. Discontinuation of treatment with epoetin theta should be taken into account.

PRCA caused by neutralising anti-erythropoietin antibodies has been reported in association with erythropoietin therapy, including with epoetin theta. These antibodies have been shown to cross-react with all epoetins, and patients suspected or confirmed to have neutralising antibodies to erythropoietin should not be switched to epoetin theta (see section 4.8).

In order to improve the traceability of epoetins, the name of the administered epoetin should be clearly recorded in the patient file.

A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin and perform anti-erythropoietin antibody testing. Cases have been reported in patients with hepatitis C treated with interferon and ribavirin, when epoetins are used concomitantly. Epoetins are not approved in the management of anaemia associated with hepatitis C.

Hypertension

Patients on epoetin theta therapy can experience an increase in blood pressure or aggravation of existing hypertension particularly during the initial treatment phase.

Therefore, in patients treated with epoetin theta, special care should be taken to monitor closely and control blood pressure. Blood pressure should be controlled adequately before initiation and during therapy to avoid acute complications, such as hypertensive crisis with encephalopathy-like symptoms (e.g. headaches, confused state, speech disturbances, impaired gait) and related complications (seizures, stroke), which may also occur in individual patients with otherwise normal or low blood pressure. If these reactions occur, they require the immediate attention of a physician and intensive medical care. Particular attention should be paid to sudden sharp migraine-like headaches as a possible warning signal.

Increases in blood pressure may require treatment with antihypertensive medicinal products or a dose increase of existing antihypertensive medicinal products. In addition, a reduction of the administered dose of epoetin theta needs to be considered. If blood pressure values remain high, temporary interruption of epoetin theta therapy may be required. Once hypertension has been controlled with more intensified therapy, epoetin theta therapy should be re-started at a reduced dose.

Misuse

Misuse of epoetin theta by healthy persons may lead to an excessive increase in haemoglobin and haematocrit. This may be associated with life-threatening cardiovascular complications.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment. More severe cases have been observed with long-acting epoetins.

At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, epoetin theta should be withdrawn immediately and an alternative treatment considered.
If the patient has developed a severe cutaneous skin reaction such as SJS or TEN due to the use of epoetin theta, treatment with epoetin theta must not be restarted in this patient at any time.

Special populations

Due to limited experience, the efficacy and safety of epoetin theta could not be assessed in patients with impaired liver function or homozygous sickle cell anaemia.
In clinical trials, patients over 75 years of age had a higher incidence of serious and severe adverse events irrespective of a causal relationship to treatment with epoetin theta. Furthermore, deaths were more frequent in this patient group compared to younger patients.

Laboratory monitoring

It is recommended that haemoglobin measurement, a complete blood count and platelet count be performed regularly.

Symptomatic anaemia associated with chronic renal failure

The use of epoetin theta in nephrosclerotic patients not yet undergoing dialysis should be defined individually, as a possible accelerated progression of renal failure cannot be ruled out with certainty.
During haemodialysis, patients treated with epoetin theta may require increased anticoagulation treatment to prevent clotting of the arterio-venous shunt.
In patients with chronic renal failure, the maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration recommended in section 4.2.
In clinical trials, an increased risk of death and serious cardiovascular events was observed when epoetins were administered to target a haemoglobin level in excess of 12 g/dl (7.45 mmol/l). Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when the haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.
Caution should be exercised with escalation of epoetin theta doses in patients with chronic renal failure since high cumulative epoetin doses may be associated with an increased risk of mortality, serious cardiovascular and cerebrovascular events. In patients with a poor haemoglobin response to epoetins, alternative explanations for the poor response should be considered (see sections 4.2 and 5.1).

Symptomatic anaemia in cancer patients with non-myeloid malignancies receiving chemotherapy

Effect on tumour growth

Epoetins are growth factors that primarily stimulate red blood cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. As with all growth factors, there is a concern that epoetins could stimulate the growth of any type of malignancy (see section 5.1).
In several controlled studies, epoetins have not been shown to improve overall survival or decrease the risk of tumour progression in patients with anaemia associated with cancer. In controlled clinical studies, use of epoetins has shown:
- shortened time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a haemoglobin level in excess of 14 g/dl (8.69 mmol/l),
- shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a haemoglobin value of 12-14 g/dl (7.45-8.69 mmol/l),

- increased risk of death when administered to target a haemoglobin value of 12 g/dl (7.45 mmol/l) in patients with active malignant disease receiving neither chemotherapy nor radiation therapy.

Epoetins are not indicated for use in this patient population.

In view of the above, in some clinical situations blood transfusion should be the preferred treatment for the management of anaemia in patients with cancer. The decision to administer recombinant erythropoietins should be based on a benefit-risk assessment with the participation of the individual patient, which should take into account the specific clinical context. Factors that should be considered in this assessment should include the type of tumour and its stage, the degree of anaemia, life-expectancy, the environment in which the patient is being treated, and patient preference (see section 5.1).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled syringe, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of epoetin theta in pregnant women. Animal studies with other epoetins do not indicate direct harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Eporatio during pregnancy.

Breast-feeding

It is unknown whether epoetin theta/metabolites are excreted in human milk, but data in neonates show no absorption or pharmacological activity of erythropoietin when given together with breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Eporatio therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No data are available.

4.7 Effects on ability to drive and use machines

Epoetin theta has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Approximately 9% of patients can be expected to experience an adverse reaction. The most frequent adverse reactions are hypertension, influenza-like illness and headache.

Tabulated list of adverse reactions

The safety of epoetin theta has been evaluated based on results from clinical studies including 972 patients.

Adverse reactions listed below in table 1 are classified according to System Organ Class. Frequency groupings are defined according to 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: Adverse reactions			
System organ class	*Adverse reaction*	*Frequency*	
		Symptomatic anaemia associated with chronic renal failure	*Symptomatic anaemia in cancer patients with non-myeloid malignancies receiving chemotherapy*
Blood and lymphatic system disorders	Pure red cell aplasia (PRCA)*	Not known	-
Immune system disorders	Hypersensitivity reactions	Not known	
Nervous system disorders	Headache	Common	
Vascular disorders	Hypertension*	Common	
	Hypertensive crisis*	Common	-
	Shunt thrombosis*	Common	-
	Thromboembolic events	-	Not known
Skin and subcutaneous tissue disorders	Skin reaction*	Common	-
Musculoskeletal and connective tissue disorders	Arthralgia	-	Common
General disorders and administration site conditions	Influenza-like illness*	Common	
*See subsection "Description of selected adverse reactions" below			

Description of selected adverse reactions

In patients with chronic renal failure, neutralising anti-erythropoietin antibody-mediated pure red cell aplasia (PRCA) associated with epoetin theta therapy has been reported in post marketing setting. If PRCA is diagnosed, therapy with epoetin theta must be discontinued and patients should not be switched to another recombinant epoetin (see section 4.4).

One of the most frequent adverse reactions during treatment with epoetin theta is an increase in blood pressure or aggravation of existing hypertension particularly during the initial treatment phase. Hypertension occurs in chronic renal failure patients more often during the correction phase than during the maintenance phase. Hypertension can be treated with appropriate medicinal products (see section 4.4).

Hypertensive crisis with encephalopathy-like symptoms (e.g. headaches, confused state, speech disturbances, impaired gait) and related complications (seizures, stroke) may also occur in individual patients with otherwise normal or low blood pressure (see section 4.4).

Shunt thrombosis may occur, especially in patients who have a tendency to hypotension or whose arterio-venous fistulae exhibit complications (e.g. stenoses, aneurisms) (see section 4.4).

Skin reactions such as rash, pruritus or injection site reactions may occur.

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment (see section 4.4).

Symptoms of influenza-like illness such as fever, chills and asthenic conditions have been reported.

4.8 Overdose

The therapeutic margin of epoetin theta is very wide. In the case of overdose, polycythaemia can occur. In the event of polycythaemia, epoetin theta should be temporarily withheld.
If severe polycythaemia occurs, conventional methods (phlebotomy) may be indicated to reduce the haemoglobin level.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antianemic preparations, ATC code: B03XA01

Mechanism of action

Human erythropoietin is an endogenous glycoprotein hormone that is the primary regulator of erythropoiesis through specific interaction with the erythropoietin receptor on the erythroid progenitor cells in the bone marrow. It acts as a mitosis-stimulating factor and differentiation hormone. The production of erythropoietin primarily occurs in and is regulated by the kidney in response to changes in tissue oxygenation. Production of endogenous erythropoietin is impaired in patients with chronic renal failure and the primary cause of their anaemia is erythropoietin deficiency. In patients with cancer receiving chemotherapy the aetiology of anaemia is multifactorial. In these patients, erythropoietin deficiency and a reduced response of erythroid progenitor cells to endogenous erythropoietin both contribute significantly towards their anaemia.
Epoetin theta is identical in its amino acid sequence and similar in its carbohydrate composition (glycosylation) to endogenous human erythropoietin.

Preclinical efficacy

The biological efficacy of epoetin theta has been demonstrated after intravenous and subcutaneous administration in various animal models in vivo (mice, rats, dogs). After administration of epoetin theta, the number of erythrocytes, the haematocrit values and reticulocyte counts increase.

Clinical efficacy and safety

Symptomatic anaemia associated chronic renal failure

Data from correction phase studies in 284 chronic renal failure patients show that the haemoglobin response rates (defined as haemoglobin levels above 11 g/dl at two consecutive measurements) in the epoetin theta group (88.4% and 89.4% in studies in patients on dialysis and not yet undergoing dialysis, respectively) were comparable to epoetin beta (86.2% and 81.0%, respectively). The median time to response was similar in the treatment groups with 56 days in haemodialysis patients and 49 days in patients not yet undergoing dialysis.
Two randomised controlled studies were conducted in 270 haemodialysis patients and 288 patients not yet undergoing dialysis, who were on stable treatment with epoetin beta. Patients were randomised to continue their current treatment or to be converted to epoetin theta (same dose as epoetin beta) in order to maintain their haemoglobin levels. During the evaluation period (weeks 15 to 26), the mean and median level of haemoglobin in patients treated with epoetin theta was virtually identical to their baseline haemoglobin level. In these two studies, 180 haemodialysis patients and 193 patients not undergoing dialysis were switched from maintenance phase treatment with epoetin beta to treatment with epoetin theta for a period of six months showing stable haemoglobin values and a similar safety profile as epoetin beta. In the clinical studies, patients not yet undergoing dialysis (subcutaneous administration) discontinued the study more frequently than haemodialysis patients (intravenous administration) as they had to terminate the study when starting dialysis.
In two long-term studies, the efficacy of epoetin theta was evaluated in 124 haemodialysis patients and 289 patients not yet undergoing dialysis. The haemoglobin levels remained within the desired target range and epoetin theta was well tolerated over a period of up to 15 months.

In the clinical studies, pre-dialysis patients were treated once-weekly with epoetin theta, 174 patients in the maintenance phase study and 111 patients in the long-term study.
Pooled post-hoc analyses of clinical studies of epoetins have been performed in chronic renal failure patients (on dialysis, not on dialysis, in diabetic and non-diabetic patients). A tendency towards increased risk estimates for all-cause mortality, cardiovascular and cerebrovascular events associated with higher cumulative epoetin doses independent of the diabetes or dialysis status was observed (see sections 4.2 and section 4.4).
Symptomatic anaemia in cancer patients with non-myeloid malignancies receiving chemotherapy
409 cancer patients receiving chemotherapy were included in two prospective, randomized double-blind, placebo-controlled studies. The first study was conducted in 186 anaemic patients with non-myeloid malignancies (55% with haematological malignancies and 45% with solid tumours) receiving non-platinum chemotherapy. The second study was conducted in 223 patients with various solid tumours receiving platinum-containing chemotherapy. In both studies, treatment with epoetin theta resulted in a significant haemoglobin response ($p < 0.001$), defined as an increase in haemoglobin of ≥ 2 g/dl without transfusion, and a significant reduction in transfusion requirements ($p < 0.05$) in comparison to placebo.
Effect on tumour growth
Erythropoietin is a growth factor that primarily stimulates red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells.
Survival and tumour progression have been examined in five large controlled studies involving a total of 2,833 patients, of which four were double-blind placebo-controlled studies and one was an openlabel study. Two of the studies recruited patients who were being treated with chemotherapy. The target haemoglobin concentration in two studies was > 13 g/dl; in the remaining three studies it was 12-14 g/dl. In the open-label study there was no difference in overall survival between patients treated with recombinant human erythropoietin and controls. In the four placebo-controlled studies the hazard ratios for overall survival ranged between 1.25 and 2.47 in favour of controls. These studies have shown a consistent unexplained statistically significant excess mortality in patients who have anaemia associated with various common cancers who received recombinant human erythropoietin compared to controls. Overall survival outcome in the trials could not be satisfactorily explained by differences in the incidence of thrombosis and related complications between those given recombinant human erythropoietin and those in the control group.
Data from three placebo-controlled clinical studies in 586 anaemic cancer patients conducted with epoetin theta, showed no negative effect of epoetin theta on survival. During the studies, mortality was lower in the epoetin theta group (6.9%) compared to placebo (10.3%).
A systematic review has also been performed involving more than 9,000 cancer patients participating in 57 clinical trials. Meta-analysis of overall survival data produced a hazard ratio point estimate of 1.08 in favour of controls (95% CI: 0.99, 1.18; 42 trials and 8,167 patients). An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06; 35 trials and 6,769 patients) was observed in patients treated with recombinant human erythropoietin. There is therefore consistent evidence to suggest that there may be significant harm to patients with cancer who are treated with recombinant human erythropoietin. The extent to which these outcomes might apply to the administration of recombinant human erythropoietin to patients with cancer, treated with chemotherapy to achieve haemoglobin concentrations less than 13 g/dl, is unclear because few patients with these characteristics were included in the data reviewed.
A patient-level data analysis has also been performed on more than 13,900 cancer patients (chemo-, radio-, chemoradio- or no therapy) participating in 53 controlled clinical trials involving several epoetins. Meta-analysis of overall survival data produced a hazard ratio point estimate of 1.06 in favour of controls (95% CI: 1.00, 1.12; 53 trials and 13,933 patients) and for

cancer patients receiving chemotherapy, the overall survival hazard ratio was 1.04 (95% CI: 0.97, 1.11; 38 trials and 10,441 patients). Meta-analyses also indicate consistently a significantly increased relative risk of thromboembolic events in cancer patients receiving recombinant human erythropoietin (see section 4.4).

5.2 Pharmacokinetic properties

General

The pharmacokinetics of epoetin theta have been examined in healthy volunteers, in patients with chronic renal failure and in cancer patients receiving chemotherapy. The pharmacokinetics of epoetin theta are independent of age or gender.

Subcutaneous administration

Following subcutaneous injection of 40 IU/kg body weight epoetin theta at three different sites (upper arm, abdomen, thigh) in healthy volunteers, similar plasma level profiles were observed. The extent of absorption (AUC) was slightly greater after injection in the abdomen in comparison to the other sites. The maximum concentration is reached after an average of 10 to 14 hours and the average terminal half-life ranges from approximately 22 to 41 hours.

Average bioavailability of epoetin theta after subcutaneous administration is approximately 31% compared with intravenous administration.

In pre-dialysis patients with chronic renal failure following subcutaneous injection of 40 IU/kg body weight, the protracted absorption results in a concentration plateau, whereby the maximum concentration is reached after an average of approximately 14 hours. The terminal half-life is higher than after intravenous administration, with an average of 25 hours after single dosing and 34 hours in steady state after repeated dosing three times weekly, without leading to an accumulation of epoetin theta.

In cancer patients receiving chemotherapy, after repeated subcutaneous administration of 20,000 IU epoetin theta once-weekly, the terminal half-life is 29 hours after the first dose and 28 hours in steady state. No accumulation of epoetin theta was observed.

Intravenous administration

In patients with chronic renal failure undergoing haemodialysis, the elimination half-life of epoetin theta is 6 hours after single dosing and 4 hours in steady state after repeated intravenous administration of 40 IU/kg body weight epoetin theta three times weekly. No accumulation of epoetin theta was observed. Following intravenous administration, the volume of distribution approximates to total blood volume.

5.3 Preclinical safety data

Non-clinical data with epoetin theta reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

Non-clinical data with other epoetins reveal no special hazard for humans based on conventional studies of genotoxicity and toxicity to reproduction.

In reproductive toxicity studies performed with other epoetins, effects interpreted as being secondary to decreased maternal body weight were observed at doses sufficiently in excess to the recommended human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate dihydrate
Sodium chloride
Polysorbate 20
Trometamol
Hydrochloric acid (6 M) (for pH adjustment)
Water for injections

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
EPORATIO 2,000 IU/0.5 ml solution for injection in pre-filled syringe
2 years
EPORATIO 3,000 IU/0.5 ml solution for injection in pre-filled syringe
2 years
EPORATIO 5,000 IU/0.5 ml solution for injection in pre-filled syringe
30 months
EPORATIO 10,000 IU/1 ml solution for injection in pre-filled syringe
30 months
EPORATIO 20,000 IU/1 ml solution for injection in pre-filled syringe
30 months
EPORATIO 30,000 IU/1 ml solution for injection in pre-filled syringe
30 months
For the purpose of ambulatory use, the patient may remove the product from the refrigerator and store it at a temperature not above 25 °C for a single period of up to 7 days without exceeding the expiry date. Once removed from the refrigerator, the medicinal product must be used within this period or disposed of.

6.4 Special precautions for storage
Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container
EPORATIO 2,000 IU/0.5 ml solution for injection in pre-filled syringe
0.5 ml solution in a pre-filled syringe (type I glass) with a tip cap (bromobutyl rubber), a plunger stopper (teflonised chlorobutyl rubber) and an injection needle (stainless steel) or an injection needle (stainless steel) with a safety shield (safety needle) or an injection needle (stainless steel) with a safety device.
Pack sizes of 6 pre-filled syringes; 6 pre-filled syringes with safety needle or 6 pre-filled syringes with safety device.
Not all pack sizes may be marketed.

EPORATIO 3,000 IU/0.5 ml solution for injection in pre-filled syringe
0.5 ml solution in a pre-filled syringe (type I glass) with a tip cap (bromobutyl rubber), a plunger stopper (teflonised chlorobutyl rubber) and an injection needle (stainless steel) or an injection needle (stainless steel) with a safety shield (safety needle) or an injection needle (stainless steel) with a safety device.
Pack sizes of 6 pre-filled syringes; 6 pre-filled syringes with safety needle or 6 pre-filled syringes with safety device.
Not all pack sizes may be marketed.

EPORATIO 5,000 IU/0.5 ml solution for injection in pre-filled syringe

0.5 ml solution in a pre-filled syringe (type I glass) with a tip cap (bromobutyl rubber), a plunger stopper (teflonised chlorobutyl rubber) and an injection needle (stainless steel) or an injection needle (stainless steel) with a safety shield (safety needle) or an injection needle (stainless steel) with a safety device.
Pack sizes of 6 pre-filled syringes; 6 pre-filled syringes with safety needle or 6 pre-filled syringes with safety device.
Not all pack sizes may be marketed.

EPORATIO 10,000 IU/1 ml solution for injection in pre-filled syringe
1 ml solution in a pre-filled syringe (type I glass) with a tip cap (bromobutyl rubber), a plunger stopper (teflonised chlorobutyl rubber) and an injection needle (stainless steel) or an injection needle (stainless steel) with a safety shield (safety needle) or an injection needle (stainless steel) with a safety device.
Pack sizes of 1, 4 and 6 pre-filled syringes; 1, 4 and 6 pre-filled syringes with safety needle or 1, 4 and 6 pre-filled syringes with safety device.
Not all pack sizes may be marketed.

EPORATIO 20,000 IU/1 ml solution for injection in pre-filled syringe
1 ml solution in a pre-filled syringe (type I glass) with a tip cap (bromobutyl rubber), a plunger stopper (teflonised chlorobutyl rubber) and an injection needle (stainless steel) or an injection needle (stainless steel) with a safety shield (safety needle) or an injection needle (stainless steel) with a safety device.

Pack sizes of 1, 4 and 6 pre-filled syringes; 1, 4 and 6 pre-filled syringes with safety needle or 1, 4 and 6 pre-filled syringes with safety device.
Not all pack sizes may be marketed.

EPORATIO 30,000 IU/1 ml solution for injection in pre-filled syringe
1 ml solution in a pre-filled syringe (type I glass) with a tip cap (bromobutyl rubber), a plunger stopper (teflonised chlorobutyl rubber) and an injection needle (stainless steel) or an injection needle (stainless steel) with a safety shield (safety needle) or an injection needle (stainless steel) with a safety device.
Pack sizes of 1, 4 and 6 pre-filled syringes; 1, 4 and 6 pre-filled syringes with safety needle or 1, 4 and
6 pre-filled syringes with safety device.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
The pre-filled syringes are for single use only.
The solution should be visually inspected prior to use. Only clear, colourless solutions without particles should be used. The solution for injection should not be shaken. It should be allowed to reach a comfortable temperature (15 °C - 25 °C) for injection.
For instructions on how to inject the medicinal product, see package leaflet.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
Manufactured and Packed by:
Merckle GmbH

Ludwig-Merckle-Straße 3
89143 Blaubeuren, Germany

Released by:
Merckle GmbH
Graf-Arco-Str.3
89079 Ulm, Germany

Imported by:
Teva Pharma (Thailand) Co., Ltd. Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF AUTHORIZATION

10. DATE OF REVISION OF THE TEXT
Feb 2021