ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 1,000 IU/0.5 ml solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled syringe containing 1,000 IU per 0.5 ml dose (2,000 IU/ml) of the active substance epoetin delta.
Epoetin delta is produced in human cells (HT-1080) by gene-activation technology.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe.
Clear, colourless and waterlike.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dynepo is indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult patients. It may be used in patients on dialysis and in patients not on dialysis.

4.2 Posology and method of administration

Treatment with Dynepo should be initiated by physicians experienced in the treatment of anaemia associated with CRF..

The dosage of Dynepo must be adjusted individually to maintain the level of haemoglobin within the target range of 10 to 12g/dl.

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. Dynepo should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid puncture of peripheral veins.

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 (6.2 mmol/l) to 12g/dL (7.5mmol/l). A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12 g/dL (7.5mmol/l) are observed, are described below (see Dose Management section below).

A rise in haemoglobin of greater than 2 g/dL (1.25 mmol/l) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Patients should be monitored closely to ensure that the lowest approved dose of Dynepo is used to provide adequate control of the symptoms of anaemia.

Dose Management

Starting dose is 50 IU/kg three times a week if administered intravenously. 50 IU/kg twice a week if administered subcutaneously.

It may not be necessary to use erythropoietin during the first three months after starting peritoneal dialysis because an increase in haemoglobin often occurs during this period.

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of Dynepo before adjusting the dose. Because of the time required for erythropoiesis, an interval of approximately 4 weeks may occur between the time of a dose adjustment (initiation, increase, decrease or discontinuation) and a significant change in haemoglobin. In consequence, dose adjustment should not be made more frequently than once a month, unless clinically indicated.

Dose should be decreased by 25 % – 50 % or treatment temporarily withdrawn and then re-introduced with a lower dosage if:
- Haemoglobin reaches ≥ 12 g/dl or
- The rate of increase of haemoglobin > 2 g/dl in any 4 week period.

Dose should be increased by 25 % – 50 % if:
- Haemoglobin falls below < 10 g/dl and
- The rate of increase of haemoglobin is below 0.7 g/dl in any 4 week period.

Administration

Dynepo may be administered intravenously or subcutaneously. Subcutaneous self administration may be used after training by a medical professional.

The required weekly dose of Dynepo is lower when Dynepo is administered subcutaneously compared to intravenously.

For subcutaneous injection, the whole length of the needle should be inserted perpendicularly into a skin fold held between thumb and forefinger, the skin fold should be held throughout the injection.

Discard the syringe after initial single use.

Special populations

Dynepo is not indicated for the management of anaemia associated with cancer.

No special dosage adjustments are required in elderly patients.
Patients with homozygous sickle cell disease and renal failure should where possible be maintained at a total haemoglobin concentration between 7 and 9 g/dl.
The experience in children is limited.
Due to limited experience, the efficacy and safety of Dynepo could not be assessed in patients with impaired liver function.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients
Uncontrolled hypertension.

4.4 Special warnings and precautions for use

In patients with chronic renal failure, 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 erythropoiesis stimulating agents (ESAs) were administered to target a haemoglobin of greater than 12 g/dL (7.5 mmol/l).

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

Hypertension

Most of patients with chronic renal failure have a history of hypertension. Patients on Dynepo therapy can experience increase in blood pressure or aggravation of existing hypertension.
Therefore, in patients treated with Dynepo, 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 like hypertensive encephalopathy and related complications (seizures, stroke). 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 anti-hypertensive medicines or dosing increase of existing anti-hypertensive medications. In addition, a reduction of the administered dose of Dynepo needs to be considered. If blood pressure values remain high, a transient interruption of Dynepo therapy may be required.
Once hypertension is controlled with more intensified therapy, Dynepo therapy should be re-started at a reduced dose.

Iron evaluation

During Dynepo therapy, absolute or functional iron deficiency may develop. This is the most common cause of an incomplete response to an erythropoietin therapy.
Therefore, prior to and during Dynepo therapy, the patient's iron stores, including transferrin saturation and serum ferritin, should be evaluated. Transferrin saturation should be at least 20 %, and ferritin should be at least 100 ng/ml. If transferrin saturation falls below 20 %, or if ferritin falls below 100 ng/ml, iron should be administered. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation and ferritin to levels that will adequately support erythropoiesis stimulated by Dynepo.
Anaemia in epoetin-resistant or hyporesponsive patients with failure to respond to 20,000 IU/week should be investigated, including referral to a haematologist.

In the iron-replete patient with an inadequate response to Dynepo therapy, the following conditions should be evaluated and treated, if appropriated:

- Infection/inflammation
- Occult blood loss
- Hyperparathyroidism/Osteitis fibrosa cystica
- Aluminium intoxication
- Haemoglobinopathies such as thalassaemia or sickle cell anaemia
- Vitamin deficiencies, i.e., folic acid or vitamin B12 deficiencies
- Haemolysis
- Malignant diseases including multiple myeloma and myelodysplastic syndrome
- Malnutrition

Laboratory monitoring

It is recommended that a complete blood count and platelet count is performed regularly.

The haemoglobin level should be determined once a week until it has stabilised in the suggested target range and the maintenance dose has been established. After any dose adjustment, the haemoglobin

should also be determined once weekly until it has stabilised in the target range. The haemoglobin level should then be monitored at regular intervals.

Serum chemistry values including creatinine and potassium should be monitored regularly during Dynepo therapy.

Other

Although it has not been observed with Dynepo, since anaphylactoid reactions may occur with erythropoietin, it is recommended that the first dose be administered under medical supervision.

The use of Dynepo in nephrosclerotic patients not yet undergoing dialysis should be defined individually, as a possible acceleration of progression of renal failure cannot be ruled out with certainty.

During haemodialysis, patients treated with Dynepo may require increased anticoagulation treatment to prevent clotting of the arterio-venous shunt.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

No interactions have been reported during treatment with Dynepo in the course of clinical trials.

4.6 Pregnancy and lactation

Pregnancy: Animal studies are insufficient with respect to effects on pregnancy (see section 5.3). The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women. In case of its use during pregnancy, concomitant iron substitution should be considered in the mother.
Lactation: It is not known whether Dynepo is excreted in human breast milk. Since many compounds are excreted in human milk, caution should be advised when Dynepo is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Approximately 10% of patients can be expected to experience an adverse drug reaction. The most common are hypertension, access related thrombosis and headache. Clinical experience with epoetins suggest hypertension and thrombosis risk may be reduced by titrating the dose to maintain haemoglobin levels between 10 to 12 g/dl.

The frequency of adverse events that were experienced during Dynepo therapy is tabulated below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Body System	**Common (>1/100, <1/10)**	**Uncommon (>1/1,000, <1/100)**	**Rare (>1/10,000, <1/1000)**
Blood and lymphatic system disorders:		Polycythaemia Thrombocytosis	
Nervous system disorders:	Headache		Convulsions
Vascular disorders:	Hypertension		
Gastrointestinal disorders:		Diarrhoea Nausea	
Skin and subcutaneous tissues disorders:		Pruritus	
General disorders and administration site conditions:	Access related thrombosis	Pain Injection site reaction (e.g. pain, haemorrhage) Flu-syndrome	

Increases in serum chemistry values including creatinine and potassium have been observed (see section 4.4).

4.9 Overdose

The maximum dose of epoetin delta that can be safely administered in single or multiple doses has not been determined.

Treatment can result in polycythaemia if the haemoglobin/haematocrit is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, treatment with epoetin delta should be temporarily withdrawn until the haemoglobin/haematocrit returns to the suggested target range. Epoetin delta can then be reintroduced with a lower dosage (see section 4.2).

If severe polycythaemia occurs, conventional methods (phlebotomy) may be indicated to decrease the haemoglobin level.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianaemic - ATC code: B03XA.

Erythropoietin is a glycoprotein that stimulates the formation of erythrocytes from precursors of the stem cell compartment. It acts as a mitosis stimulating factor and differentiation hormone.

The biological efficacy of erythropoietin has been demonstrated after intravenous and subcutaneous administration in various animal models in vivo (rats and dogs). After administration of epoetin delta, the number of erythrocytes, the Hb values and reticulocyte counts increase as well as the 59Fe-incorporation rate.

During the clinical trials, there were no indications of development of neutralising antibodies to

epoetin delta in humans based on the clinical response.

When administration is halted, the eyrthropoietic parameters return toward baseline levels within the recovery period of 1-3 months. Subcutaneous administration results in a similar pattern of erythropoietic stimulation as after intravenous administration.

Patients with cancer

Dynepo is not indicated for the management of anaemia associated with cancer.

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 of epoetin alfa, beta and darbepoetin alfa involving a total of 2,833 patients, of which four were double-blind placebo-controlled studies and one was an open-label 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.

A systematic review has also been performed involving more than 9000 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 8167 patients). An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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. Survival outcomes and tumour progression in cancer patients that are being treated with Dynepo for anaemia associated with chronic renal failure have not been investigated. The extent to which the outcomes observed in the clinical studies discussed above may apply to this patient population is unclear, specifically considering that the dosages administered in the renal indication are lower than in the cancer indication.

5.2 Pharmacokinetic properties

The pharmacokinetics of erythropoietin following administration of epoetin delta has been examined in both healthy volunteers and patients with chronic renal failure. Following intravenous doses, volume of distribution approximates total blood volume and ranges from 0.063 to 0.097 l/kg. The elimination half-life ranges from 4.7 to 13.2 hours in patients. Half life is approximately 50% shorter in healthy subjects. Measurable concentrations of erythropoietin are maintained in the serum for at least 24 hours following doses ranging from 50 IU/kg to 300 IU/kg. Exposure to erythropoietin following administration of epoetin delta increases proportionately in patients given intravenous doses of 50 IU/kg to 300 IU/kg. No accumulation of epoetin delta was observed after repeated intravenous administration three times weekly.

Peak serum concentrations for subcutaneously administered epoetin delta occur between 8 and 36 hours following injection. The half-life of subcutaneously administered epoetin delta is prolonged compared to intravenous administration and ranges from 27 to 33 hours in patients. The bioavailability of subcutaneously administered epoetin delta is between 26% and 36%.

5.3 Preclinical safety data

Animal studies conducted with both Dynepo and epoetin alfa in pregnant female rats and rabbits did not show any teratogenic effect, but indicated class-related reversible effects on growth and haematopoiesis in the offspring.
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate monobasic, monohydrate
Sodium phosphate dibasic, heptahydrate
Polysorbate 20
Sodium chloride
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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 C – 8 C). Do not freeze. Keep the syringes in the outer carton to protect from light.

Unopened pre-filled syringes may be kept un-refrigerated but below 25°C for a single maximum period of 5 days. The revised expiry date for storage at below 25°C must not exceed the expiry date set in accordance with the 24 month shelf-life. Following 5 days storage at below 25°C the pre-filled syringes must be discarded.

6.5 Nature and contents of container

Prefilled Type I glass syringe with bromobutyl rubber stopper, 27 gauge stainless steel needle with rigid natural rubber and polystyrene needle shield, polystyrene plunger rod and a needle safety guard. Packs of 6 pre-filled syringes are available.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

When given subcutaneously, the site of injection should be rotated with each administration.

Inspect the pre-filled syringe before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency.
Do not shake the syringe. Prolonged vigorous shaking may denature the active substance.

The syringe is pre-assembled with a needle safety guard to prevent needle stick injury. This does not

affect normal operation of the syringe and the syringe can be rotated in the device. Administer the amount required.. When the injection has been administered the needle safety guard will cover the needle when releasing the plunger. Allow the syringe to move up until the entire needle is guarded.

7. MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/001

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 March 2002
Date of last renewal: 18 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 2,000 IU/0.5 ml solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled syringe containing 2,000 IU per 0.5 ml dose (4,000 IU/ml) of the active substance epoetin delta.
Epoetin delta is produced in human cells (HT-1080) by gene-activation technology.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe
Clear, colourless and waterlike.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dynepo is indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult patients. It may be used in patients on dialysis and in patients not on dialysis.

4.2 Posology and method of administration

Treatment with Dynepo should be initiated by physicians experienced in the treatment of anaemia associated with CRF.

The dosage of Dynepo must be adjusted individually to maintain the level of haemoglobin within the target range of 10 to 12g/dl.

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. Dynepo should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid puncture of peripheral veins.

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 (6.2 mmol/l) to 12g/dL (7.5mmol/l). A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12 g/dL (7.5mmol/l) are observed, are described below (see Dose Management section below).

A rise in haemoglobin of greater than 2 g/dL (1.25 mmol/l) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Patients should be monitored closely to ensure that the lowest approved dose of Dynepo is used to provide adequate control of the symptoms of anaemia.

Dose Management

Starting dose is 50 IU/kg three times a week if administered intravenously. 50 IU/kg twice a week if administered subcutaneously.

It may not be necessary to use erythropoietin during the first three months after starting peritoneal dialysis because an increase in haemoglobin often occurs during this period.

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of Dynepo before adjusting the dose. Because of the time required for erythropoiesis, an interval of approximately 4 weeks may occur between the time of a dose adjustment (initiation, increase, decrease or discontinuation) and a significant change in haemoglobin. In consequence, dose adjustment should not be made more frequently than once a month, unless clinically indicated.

Dose should be decreased by 25 % – 50 % or treatment temporarily withdrawn and then re-introduced with a lower dosage if:
- Haemoglobin reaches ≥ 12 g/dl or
- The rate of increase of haemoglobin > 2 g/dl in any 4 week period.

Dose should be increased by 25 % – 50 % if:
- Haemoglobin falls below < 10 g/dl and
- The rate of increase of haemoglobin is below 0.7 g/dl in any 4 week period.

Administration

Dynepo may be administered intravenously or subcutaneously. Subcutaneous self administration may be used after training by a medical professional.

The required weekly dose of Dynepo is lower when Dynepo is administered subcutaneously compared to intravenously.

For subcutaneous injection, the whole length of the needle should be inserted perpendicularly into a skin fold held between thumb and forefinger, the skin fold should be held throughout the injection.

Discard the syringe after initial single use.

Special populations

Dynepo is not indicated for the management of anaemia associated with cancer.

No special dosage adjustments are required in elderly patients.
Patients with homozygous sickle cell disease and renal failure should where possible be maintained at a total haemoglobin concentration between 7 and 9 g/dl.
The experience in children is limited.
Due to limited experience, the safety and efficacy of Dynepo could not be assessed in patients with impaired liver function.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients.
Uncontrolled hypertension.

4.4 Special warnings and precautions for use

In patients with chronic renal failure, 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 erythropoiesis stimulating agents (ESAs) were administered to target a haemoglobin of greater than 12 g/dL (7.5 mmol/l).

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

Hypertension

Most of patients with chronic renal failure have a history of hypertension. Patients on Dynepo therapy can experience increase in blood pressure or aggravation of existing hypertension.
Therefore, in patients treated with Dynepo, 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 like hypertensive encephalopathy and related complications (seizures, stroke). 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 anti-hypertensive medicines or dosing increase of existing anti-hypertensive medications. In addition, a reduction of the administered dose of Dynepo needs to be considered. If blood pressure values remain high, a transient interruption of Dynepo therapy may be required.
Once hypertension is controlled with more intensified therapy, Dynepo therapy should be re-started at a reduced dose.

Iron evaluation

During Dynepo therapy, absolute or functional iron deficiency may develop. This is the most common cause of an incomplete response to an erythropoietin therapy.
Therefore, prior to and during Dynepo therapy, the patient's iron stores, including transferrin saturation and serum ferritin, should be evaluated. Transferrin saturation should be at least 20 %, and ferritin should be at least 100 ng/ml. If transferrin saturation falls below 20 %, or if ferritin falls below 100 ng/ml, iron should be administered. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation and ferritin to levels that will adequately support erythropoiesis stimulated by Dynepo.
Anaemia in epoetin-resistant or hyporesponsive patients with failure to respond to 20,000 IU/week should be investigated, including referral to a haematologist.

In the iron-replete patient with an inadequate response to Dynepo therapy, the following conditions should be evaluated and treated, if appropriated:

- Infection/inflammation
- Occult blood loss
- Hyperparathyroidism/Osteitis fibrosa cystica
- Aluminium intoxication
- Haemoglobinopathies such as thalassaemia or sickle cell anaemia
- Vitamin deficiencies, i.e., folic acid or vitamin B12 deficiencies
- Haemolysis
- Malignant diseases including multiple myeloma and myelodysplastic syndrome
- Malnutrition

Laboratory monitoring

It is recommended that a complete blood count and platelet count is performed regularly.

The haemoglobin level should be determined once a week until it has stabilised in the suggested target range and the maintenance dose has been established. After any dose adjustment, the haemoglobin

should also be determined once weekly until it has stabilised in the target range. The haemoglobin level should then be monitored at regular intervals.

Serum chemistry values including creatinine and potassium should be monitored regularly during Dynepo therapy.

Other

Although it has not been observed with Dynepo, since anaphylactoid reactions may occur with erythropoietin, it is recommended that the first dose be administered under medical supervision.

The use of Dynepo in nephrosclerotic patients not yet undergoing dialysis should be defined individually, as a possible acceleration of progression of renal failure cannot be ruled out with certainty.

During haemodialysis, patients treated with Dynepo may require increased anticoagulation treatment to prevent clotting of the arterio-venous shunt.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

No interactions have been reported during treatment with Dynepo in the course of clinical trials.

4.6 Pregnancy and lactation

Pregnancy: Animal studies are insufficient with respect to effects on pregnancy (see section 5.3). The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women. In case of its use during pregnancy, concomitant iron substitution should be considered in the mother.
Lactation: It is not known whether Dynepo is excreted in human breast milk. Since many compounds are excreted in human milk, caution should be advised when Dynepo is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Approximately 10% of patients can be expected to experience an adverse drug reaction. The most common are hypertension, access related thrombosis and headache. Clinical experience with epoetins suggest hypertension and thrombosis risk may be reduced by titrating the dose to maintain haemoglobin levels between 10 to 12 g/dl.

The frequency of adverse events that were experienced during Dynepo therapy is tabulated below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Body System	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1000)
Blood and lymphatic system disorders:		Polycythaemia Thrombocytosis	
Nervous system disorders:	Headache		Convulsions
Vascular disorders:	Hypertension		
Gastrointestinal disorders:		Diarrhoea Nausea	
Skin and subcutaneous tissues disorders:		Pruritus	
General disorders and administration site conditions:	Access related thrombosis	Pain Injection site reaction (e.g. pain, haemorrhage) Flu-syndrome	

Increases in serum chemistry values including creatinine and potassium have been observed (see section 4.4).

4.9 Overdose

The maximum dose of epoetin delta that can be safely administered in single or multiple doses has not been determined.
Treatment can result in polycythaemia if the haemoglobin/haematocrit is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, treatment with epoetin delta should be temporarily withdrawn until the haemoglobin/haematocrit returns to the suggested target range. Epoetin delta can then be reintroduced with a lower dosage (see section 4.2).

If severe polycythaemia occurs, conventional methods (phlebotomy) may be indicated to decrease the haemoglobin level.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianaemic - ATC code: B03XA.

Erythropoietin is a glycoprotein that stimulates the formation of erythrocytes from precursors of the stem cell compartment. It acts as a mitosis stimulating factor and differentiation hormone.

The biological efficacy of erythropoietin has been demonstrated after intravenous and subcutaneous administration in various animal models in vivo (rats and dogs). After administration of epoetin delta, the number of erythrocytes, the Hb values and reticulocyte counts increase as well as the 59Fe-incorporation rate.

During the clinical trials, there were no indications of development of neutralising antibodies to epoetin delta in humans based on the clinical response.

When administration is halted, the eyrthropoietic parameters return toward baseline levels within the recovery period of 1-3 months. Subcutaneous administration results in a similar pattern of erythropoietic stimulation as after intravenous administration.

Patients with cancer

Dynepo is not indicated for the management of anaemia associated with cancer.

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 of epoetin alfa, beta and darbepoetin alfa involving a total of 2,833 patients, of which four were double-blind placebo-controlled studies and one was an open-label 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.

A systematic review has also been performed involving more than 9000 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 8167 patients). An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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. Survival outcomes and tumour progression in cancer patients that are being treated with Dynepo for anaemia associated with chronic renal failure have not been investigated. The extent to which the outcomes observed in the clinical studies discussed above may apply to this patient population is unclear, specifically considering that the dosages administered in the renal indication are lower than in the cancer indication.

5.2 Pharmacokinetic properties

The pharmacokinetics of erythropoietin following administration of epoetin delta has been examined in both healthy volunteers and patients with chronic renal failure. Following intravenous doses, volume of distribution approximates total blood volume and ranges from 0.063 to 0.097 l/kg. The elimination half-life ranges from 4.7 to 13.2 hours in patients. Half life is approximately 50% shorter in healthy subjects. Measurable concentrations of erythropoietin are maintained in the serum for at least 24 hours following doses ranging from 50 IU/kg to 300 IU/kg. Exposure to erythropoietin following administration of epoetin delta increases proportionately in patients given intravenous doses of 50 IU/kg to 300 IU/kg. No accumulation of epoetin delta was observed after repeated intravenous administration three times weekly.
Peak serum concentrations for subcutaneously administered epoetin delta occur between 8 and 36 hours following injection. The half-life of subcutaneously administered epoetin delta is prolonged compared to intravenous administration and ranges from 27 to 33 hours in patients. The bioavailability of subcutaneously administered epoetin delta is between 26% and 36%.

5.3 Preclinical safety data

Animal studies conducted with both Dynepo and epoetin alfa in pregnant female rats and rabbits did not show any teratogenic effect, but indicated class-related reversible effects on growth and haematopoiesis in the offspring.
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate monobasic, monohydrate
Sodium phosphate dibasic, heptahydrate
Polysorbate 20
Sodium chloride
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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 C – 8 C). Do not freeze. Keep the syringes in the outer carton to protect from light.

Unopened pre-filled syringes may be kept un-refrigerated but below 25°C for a single maximum period of 5 days. The revised expiry date for storage at below 25°C must not exceed the expiry date set in accordance with the 24 month shelf-life. Following 5 days storage at below 25°C the pre-filled syringes must be discarded.

6.5 Nature and contents of container

Prefilled Type I glass syringe with bromobutyl rubber stopper, 27 gauge stainless steel needle with rigid natural rubber and polystyrene needle shield, polystyrene plunger rod and a needle safety guard. Packs of 6 pre-filled syringes are available.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

When given subcutaneously, the site of injection should be rotated with each administration.

Inspect the pre-filled syringe before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency.
Do not shake the syringe. Prolonged vigorous shaking may denature the active substance.

The syringe is pre-assembled with a needle safety guard to prevent needle stick injury. This does not affect normal operation of the syringe and the syringe can be rotated in the device.. When the injection has been administered the needle safety guard will cover the needle when releasing the plunger. Allow the syringe to move up until the entire needle is guarded.

7. MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/002

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 March 2002
Date of last renewal: 18 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 3,000 IU/0.3 ml solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled syringe containing 3,000 IU per 0.3 ml dose (10,000 IU/ml) of the active substance epoetin delta.
Epoetin delta is produced in human cells (HT-1080) by gene-activation technology.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe
Clear, colourless and waterlike.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dynepo is indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult patients. It may be used in patients on dialysis and in patients not on dialysis.

4.2 Posology and method of administration

Treatment with Dynepo should be initiated by physicians experienced in the treatment of anaemia associated with CRF.

The dosage of Dynepo must be adjusted individually to maintain the level of haemoglobin within the target range of 10 to 12g/dl.

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. Dynepo should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid puncture of peripheral veins.

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 (6.2 mmol/l) to 12g/dL (7.5mmol/l). A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12 g/dL (7.5mmol/l) are observed, are described below (see Dose Management section below).

A rise in haemoglobin of greater than 2 g/dL (1.25 mmol/l) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Patients should be monitored closely to ensure that the lowest approved dose of Dynepo is used to provide adequate control of the symptoms of anaemia.

Dose Management

Starting dose is 50 IU/kg three times a week if administered intravenously. 50 IU/kg twice a week if administered subcutaneously.

It may not be necessary to use erythropoietin during the first three months after starting peritoneal dialysis because an increase in haemoglobin often occurs during this period.

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of Dynepo before adjusting the dose. Because of the time required for erythropoiesis, an interval of approximately 4 weeks may occur between the time of a dose adjustment (initiation, increase, decrease or discontinuation) and a significant change in haemoglobin. In consequence, dose adjustment should not be made more frequently than once a month, unless clinically indicated.

Dose should be decreased by 25 % – 50 % or treatment temporarily withdrawn and then re-introduced with a lower dosage if:
- Haemoglobin reaches ≥ 12 g/dl or
- The rate of increase of haemoglobin > 2 g/dl in any 4 week period.

Dose should be increased by 25 % – 50 % if:
- Haemoglobin falls below < 10 g/dl and
- The rate of increase of haemoglobin is below 0.7 g/dl in any 4 week period.

Administration

Dynepo may be administered intravenously or subcutaneously. Subcutaneous self administration may be used after training by a medical professional.

The required weekly dose of Dynepo is lower when Dynepo is administered subcutaneously compared to intravenously.

For subcutaneous injection, the whole length of the needle should be inserted perpendicularly into a skin fold held between thumb and forefinger, the skin fold should be held throughout the injection.

Discard the syringe after initial single use.

Special populations

Dynepo is not indicated for the management of anaemia associated with cancer.

No special dosage adjustments are required in elderly patients.
Patients with homozygous sickle cell disease and renal failure should where possible be maintained at a total haemoglobin concentration between 7 and 9 g/dl.
The experience in children is limited.
Due to limited experience, the safety and efficacy of Dynepo could not be assessed in patients with impaired liver function.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients.
Uncontrolled hypertension.

4.4 Special warnings and precautions for use

In patients with chronic renal failure, 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 erythropoiesis stimulating agents (ESAs) were administered to target a haemoglobin of greater than 12 g/dL (7.5 mmol/l).

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

Hypertension

Most of patients with chronic renal failure have a history of hypertension. Patients on Dynepo therapy can experience increase in blood pressure or aggravation of existing hypertension.
Therefore, in patients treated with Dynepo, 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 like hypertensive encephalopathy and related complications (seizures, stroke). 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 anti-hypertensive medicines or dosing increase of existing anti-hypertensive medications. In addition, a reduction of the administered dose of Dynepo needs to be considered. If blood pressure values remain high, a transient interruption of Dynepo therapy may be required.
Once hypertension is controlled with more intensified therapy, Dynepo therapy should be re-started at a reduced dose.

Iron evaluation

During Dynepo therapy, absolute or functional iron deficiency may develop. This is the most common cause of an incomplete response to an erythropoietin therapy.
Therefore, prior to and during Dynepo therapy, the patient's iron stores, including transferrin saturation and serum ferritin, should be evaluated. Transferrin saturation should be at least 20 %, and ferritin should be at least 100 ng/ml. If transferrin saturation falls below 20 %, or if ferritin falls below 100 ng/ml, iron should be administered. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation and ferritin to levels that will adequately support erythropoiesis stimulated by Dynepo.
Anaemia in epoetin-resistant or hyporesponsive patients with failure to respond to 20,000 IU/week should be investigated, including referral to a haematologist.

In the iron-replete patient with an inadequate response to Dynepo therapy, the following conditions should be evaluated and treated, if appropriated:

- Infection/inflammation
- Occult blood loss
- Hyperparathyroidism/Osteitis fibrosa cystica
- Aluminium intoxication
- Haemoglobinopathies such as thalassaemia or sickle cell anaemia
- Vitamin deficiencies, i.e., folic acid or vitamin B12 deficiencies
- Haemolysis
- Malignant diseases including multiple myeloma and myelodysplastic syndrome
- Malnutrition

Laboratory monitoring

It is recommended that a complete blood count and platelet count is performed regularly.

The haemoglobin level should be determined once a week until it has stabilised in the suggested target range and the maintenance dose has been established. After any dose adjustment, the haemoglobin should also be determined once weekly until it has stabilised in the target range. The haemoglobin level should then be monitored at regular intervals.

Serum chemistry values including creatinine and potassium should be monitored regularly during Dynepo therapy.

Other

Although it has not been observed with Dynepo, since anaphylactoid reactions may occur with erythropoietin, it is recommended that the first dose be administered under medical supervision.

The use of Dynepo in nephrosclerotic patients not yet undergoing dialysis should be defined individually, as a possible acceleration of progression of renal failure cannot be ruled out with certainty.

During haemodialysis, patients treated with Dynepo may require increased anticoagulation treatment to prevent clotting of the arterio-venous shunt.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

No interactions have been reported during treatment with Dynepo in the course of clinical trials.

4.6 Pregnancy and lactation

Pregnancy: Animal studies are insufficient with respect to effects on pregnancy (see section 5.3). The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women. In case of its use during pregnancy, concomitant iron substitution should be considered in the mother.
Lactation: It is not known whether Dynepo is excreted in human breast milk. Since many compounds are excreted in human milk, caution should be advised when Dynepo is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Approximately 10% of patients can be expected to experience an adverse drug reaction. The most common are hypertension, access related thrombosis and headache. Clinical experience with epoetins suggest hypertension and thrombosis risk may be reduced by titrating the dose to maintain haemoglobin levels between 10 to 12 g/dl.

The frequency of adverse events that were experienced during Dynepo therapy is tabulated below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Body System	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1000)
Blood and lymphatic system disorders:		Polycythaemia Thrombocytosis	
Nervous system disorders:	Headache		Convulsions
Vascular disorders:	Hypertension		
Gastrointestinal disorders:		Diarrhoea Nausea	
Skin and subcutaneous tissues disorders:		Pruritus	
General disorders and administration site conditions:	Access related thrombosis	Pain Injection site reaction (e.g. pain, haemorrhage) Flu-syndrome	

Increases in serum chemistry values including creatinine and potassium have been observed (see section 4.4).

4.9 Overdose

The maximum dose of epoetin delta that can be safely administered in single or multiple doses has not been determined.

Treatment can result in polycythaemia if the haemoglobin/haematocrit is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, treatment with epoetin delta should be temporarily withdrawn until the haemoglobin/haematocrit returns to the suggested target range. Epoetin delta can then be reintroduced with a lower dosage (see section 4.2).

If severe polycythaemia occurs, conventional methods (phlebotomy) may be indicated to decrease the haemoglobin level.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianaemic - ATC code: B03XA..

Erythropoietin is a glycoprotein that stimulates the formation of erythrocytes from precursors of the stem cell compartment. It acts as a mitosis stimulating factor and differentiation hormone.

The biological efficacy of erythropoietin has been demonstrated after intravenous and subcutaneous administration in various animal models in vivo (rats and dogs). After administration of epoetin delta, the number of erythrocytes, the Hb values and reticulocyte counts increase as well as the 59Fe-incorporation rate.

During the clinical trials, there were no indications of development of neutralising antibodies to epoetin delta in humans based on the clinical response.

When administration is halted, the eyrthropoietic parameters return toward baseline levels within the recovery period of 1-3 months. Subcutaneous administration results in a similar pattern of erythropoietic stimulation as after intravenous administration.

Patients with cancer

Dynepo is not indicated for the management of anaemia associated with cancer.

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 of epoetin alfa, beta and darbepoetin alfa involving a total of 2,833 patients, of which four were double-blind placebo-controlled studies and one was an open-label 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.

A systematic review has also been performed involving more than 9000 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 8167 patients). An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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. Survival outcomes and tumour progression in cancer patients that are being treated with Dynepo for anaemia associated with chronic renal failure have not been investigated. The extent to which the outcomes observed in the clinical studies discussed above may apply to this patient population is unclear, specifically considering that the dosages administered in the renal indication are lower than in the cancer indication.

5.2 Pharmacokinetic properties

The pharmacokinetics of erythropoietin following administration of epoetin delta has been examined in both healthy volunteers and patients with chronic renal failure. Following intravenous doses, volume of distribution approximates total blood volume and ranges from 0.063 to 0.097 l/kg. The elimination half-life ranges from 4.7 to 13.2 hours in patients. Half life is approximately 50% shorter in healthy subjects. Measurable concentrations of erythropoietin are maintained in the serum for at least 24 hours following doses ranging from 50 IU/kg to 300 IU/kg. Exposure to erythropoietin following administration of epoetin delta increases proportionately in patients given intravenous doses of 50 IU/kg to 300 IU/kg. No accumulation of epoetin delta was observed after repeated intravenous administration three times weekly.
Peak serum concentrations for subcutaneously administered epoetin delta occur between 8 and 36 hours following injection. The half-life of subcutaneously administered epoetin delta is prolonged compared to intravenous administration and ranges from 27 to 33 hours in patients.

The bioavailability of subcutaneously administered epoetin delta is between 26% and 36%.

5.3 Preclinical safety data

Animal studies conducted with both Dynepo and epoetin alfa in pregnant female rats and rabbits did not show any teratogenic effect, but indicated class-related reversible effects on growth and haematopoiesis in the offspring.
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate monobasic, monohydrate
Sodium phosphate dibasic, heptahydrate
Polysorbate 20
Sodium chloride
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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 C – 8 C). Do not freeze. Keep the syringes in the outer carton to protect from light.

Unopened pre-filled syringes may be kept un-refrigerated but below 25°C for a single maximum period of 5 days. The revised expiry date for storage at below 25°C must not exceed the expiry date set in accordance with the 24 month shelf-life. Following 5 days storage at below 25°C the pre-filled syringes must be discarded.

6.5 Nature and contents of container

Prefilled Type I glass syringe with bromobutyl rubber stopper, 27 gauge stainless steel needle with rigid natural rubber and polystyrene needle shield, polystyrene plunger rod and a needle safety guard. Packs of 6 pre-filled syringes are available.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

When given subcutaneously, the site of injection should be rotated with each administration.

Inspect the pre-filled syringe before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency.
Do not shake the syringe. Prolonged vigorous shaking may denature the active substance.

The syringe is pre-assembled with a needle safety guard to prevent needle stick injury. This does not affect normal operation of the syringe and the syringe can be rotated in the device. When the injection has been administered the needle safety guard will cover the needle when releasing the plunger. Allow the syringe to move up until the entire needle is guarded.

7. MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/003

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 March 2002
Date of last renewal: 18 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 4,000 IU/0.4 ml solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled syringe containing 4,000 IU per 0.4 ml dose (10,000 IU/ml) of the active substance epoetin delta.
Epoetin delta is produced in human cells (HT-1080) by gene-activation technology.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe
Clear, colourless and waterlike.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dynepo is indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult patients. It may be used in patients on dialysis and in patients not on dialysis.

4.2 Posology and method of administration

Treatment with Dynepo should be initiated by physicians experienced in the treatment of anaemia associated with CRF.

The dosage of Dynepo must be adjusted individually to maintain the level of haemoglobin within the target range of 10 to 12g/dl.

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. Dynepo should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid puncture of peripheral veins.

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 (6.2 mmol/l) to 12g/dL (7.5mmol/l). A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12 g/dL (7.5mmol/l) are observed, are described below (see Dose Management section below).

A rise in haemoglobin of greater than 2 g/dL (1.25 mmol/l) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Patients should be monitored closely to ensure that the lowest approved dose of Dynepo is used to provide adequate control of the symptoms of anaemia.

Dose Management

Starting dose is 50 IU/kg three times a week if administered intravenously. 50 IU/kg twice a week if administered subcutaneously.

It may not be necessary to use erythropoietin during the first three months after starting peritoneal dialysis because an increase in haemoglobin often occurs during this period.

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of Dynepo before adjusting the dose. Because of the time required for erythropoiesis, an interval of approximately 4 weeks may occur between the time of a dose adjustment (initiation, increase, decrease or discontinuation) and a significant change in haemoglobin. In consequence, dose adjustment should not be made more frequently than once a month, unless clinically indicated.

Dose should be decreased by 25 % – 50 % or treatment temporarily withdrawn and then re-introduced with a lower dosage if:
- Haemoglobin reaches ≥ 12 g/dl or
- The rate of increase of haemoglobin > 2 g/dl in any 4 week period.

Dose should be increased by 25 % – 50 % if:
- Haemoglobin falls below < 10 g/dl and
- The rate of increase of haemoglobin is below 0.7 g/dl in any 4 week period.

Administration

Dynepo may be administered intravenously or subcutaneously. Subcutaneous self administration may be used after training by a medical professional.

The required weekly dose of Dynepo is lower when Dynepo is administered subcutaneously compared to intravenously.

For subcutaneous injection, the whole length of the needle should be inserted perpendicularly into a skin fold held between thumb and forefinger, the skin fold should be held throughout the injection.

Discard the syringe after initial single use.

Special populations

Dynepo is not indicated for the management of anaemia associated with cancer.

No special dosage adjustments are required in elderly patients.
Patients with homozygous sickle cell disease and renal failure should where possible be maintained at a total haemoglobin concentration between 7 and 9 g/dl.
The experience in children is limited
Due to limited experience, the safety and efficacy of Dynepo could not be assessed in patients with impaired liver function.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients.
Uncontrolled hypertension.

4.4 Special warnings and precautions for use

In patients with chronic renal failure, 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 erythropoiesis stimulating agents (ESAs) were administered to target a haemoglobin of greater than 12 g/dL (7.5 mmol/l).

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

Hypertension

Most of patients with chronic renal failure have a history of hypertension. Patients on Dynepo therapy can experience increase in blood pressure or aggravation of existing hypertension.
Therefore, in patients treated with Dynepo, 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 like hypertensive encephalopathy and related complications (seizures, stroke). 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 anti-hypertensive medicines or dosing increase of existing anti-hypertensive medications. In addition, a reduction of the administered dose of Dynepo needs to be considered. If blood pressure values remain high, a transient interruption of Dynepo therapy may be required.
Once hypertension is controlled with more intensified therapy, Dynepo therapy should be re-started at a reduced dose.

Iron evaluation

During Dynepo therapy, absolute or functional iron deficiency may develop. This is the most common cause of an incomplete response to an erythropoietin therapy.
Therefore, prior to and during Dynepo therapy, the patient's iron stores, including transferrin saturation and serum ferritin, should be evaluated. Transferrin saturation should be at least 20 %, and ferritin should be at least 100 ng/ml. If transferrin saturation falls below 20 %, or if ferritin falls below 100 ng/ml, iron should be administered. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation and ferritin to levels that will adequately support erythropoiesis stimulated by Dynepo.
Anaemia in epoetin-resistant or hyporesponsive patients with failure to respond to 20,000 IU/week should be investigated, including referral to a haematologist.

In the iron-replete patient with an inadequate response to Dynepo therapy, the following conditions should be evaluated and treated, if appropriated:

- Infection/inflammation
- Occult blood loss
- Hyperparathyroidism/Osteitis fibrosa cystica
- Aluminium intoxication
- Haemoglobinopathies such as thalassaemia or sickle cell anaemia
- Vitamin deficiencies, i.e., folic acid or vitamin B12 deficiencies
- Haemolysis
- Malignant diseases including multiple myeloma and myelodysplastic syndrome
- Malnutrition

Laboratory monitoring

It is recommended that a complete blood count and platelet count is performed regularly.

The haemoglobin level should be determined once a week until it has stabilised in the suggested target range and the maintenance dose has been established. After any dose adjustment, the haemoglobin should also be determined once weekly until it has stabilised in the target range. The haemoglobin level should then be monitored at regular intervals.

Serum chemistry values including creatinine and potassium should be monitored regularly during Dynepo therapy.

Other:

Although it has not been observed with Dynepo, since anaphylactoid reactions may occur with erythropoietin, it is recommended that the first dose be administered under medical supervision.

The use of Dynepo in nephrosclerotic patients not yet undergoing dialysis should be defined individually, as a possible acceleration of progression of renal failure cannot be ruled out with certainty.

During haemodialysis, patients treated with Dynepo may require increased anticoagulation treatment to prevent clotting of the arterio-venous shunt.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

No interactions have been reported during treatment with Dynepo in the course of clinical trials.

4.6 Pregnancy and lactation

Pregnancy: Animal studies are insufficient with respect to effects on pregnancy (see section 5.3). The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women. In case of its use during pregnancy, concomitant iron substitution should be considered in the mother.
Lactation: It is not known whether Dynepo is excreted in human breast milk. Since many compounds are excreted in human milk, caution should be advised when Dynepo is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Approximately 10% of patients can be expected to experience an adverse drug reaction. The most common are hypertension, access related thrombosis and headache. Clinical experience with epoetins suggest hypertension and thrombosis risk may be reduced by titrating the dose to maintain haemoglobin levels between 10 to 12 g/dl.

The frequency of adverse events that were experienced during Dynepo therapy is tabulated below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Body System	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1000)
Blood and lymphatic system disorders:		Polycythaemia Thrombocytosis	
Nervous system disorders:	Headache		Convulsions
Vascular disorders:	Hypertension		
Gastrointestinal disorders:		Diarrhoea Nausea	
Skin and subcutaneous tissues disorders:		Pruritus	
General disorders and administration site conditions:	Access related thrombosis	Pain Injection site reaction (e.g. pain, haemorrhage) Flu-syndrome	

Increases in serum chemistry values including creatinine and potassium have been observed (see section 4.4).

4.9 Overdose

The maximum dose of epoetin delta that can be safely administered in single or multiple doses has not been determined.

Treatment can result in polycythaemia if the haemoglobin/haematocrit is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, treatment with epoetin delta should be temporarily withdrawn until the haemoglobin/haematocrit returns to the suggested target range. Epoetin delta can then be reintroduced with a lower dosage (see section 4.2).

If severe polycythaemia occurs, conventional methods (phlebotomy) may be indicated to decrease the haemoglobin level.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianaemic - ATC code: B03XA..

Erythropoietin is a glycoprotein that stimulates the formation of erythrocytes from precursors of the stem cell compartment. It acts as a mitosis stimulating factor and differentiation hormone.

The biological efficacy of erythropoietin has been demonstrated after intravenous and subcutaneous administration in various animal models in vivo (rats and dogs). After administration of epoetin delta, the number of erythrocytes, the Hb values and reticulocyte counts increase as well as the 59Fe-incorporation rate.

During the clinical trials, there were no indications of development of neutralising antibodies to epoetin delta in humans based on the clinical response.

When administration is halted, the eyrthropoietic parameters return toward baseline levels within the recovery period of 1-3 months. Subcutaneous administration results in a similar pattern of erythropoietic stimulation as after intravenous administration.

Patients with cancer

Dynepo is not indicated for the management of anaemia associated with cancer.

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 of epoetin alfa, beta and darbepoetin alfa involving a total of 2,833 patients, of which four were double-blind placebo-controlled studies and one was an open-label 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.

A systematic review has also been performed involving more than 9000 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 8167 patients). An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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. Survival outcomes and tumour progression in cancer patients that are being treated with Dynepo for anaemia associated with chronic renal failure have not been investigated. The extent to which the outcomes observed in the clinical studies discussed above may apply to this patient population is unclear, specifically considering that the dosages administered in the renal indication are lower than in the cancer indication.

5.2 Pharmacokinetic properties

The pharmacokinetics of erythropoietin following administration of epoetin delta has been examined in both healthy volunteers and patients with chronic renal failure. Following intravenous doses, volume of distribution approximates total blood volume and ranges from 0.063 to 0.097 l/kg. The elimination half-life ranges from 4.7 to 13.2 hours in patients. Half life is approximately 50% shorter in healthy subjects. Measurable concentrations of erythropoietin are maintained in the serum for at least 24 hours following doses ranging from 50 IU/kg to 300 IU/kg. Exposure to erythropoietin following administration of epoetin delta increases proportionately in patients given intravenous doses of 50 IU/kg to 300 IU/kg. No accumulation of epoetin delta was observed after repeated intravenous administration three times weekly.
Peak serum concentrations for subcutaneously administered epoetin delta occur between 8 and 36 hours following injection. The half-life of subcutaneously administered epoetin delta is prolonged compared to intravenous administration and ranges from 27 to 33 hours in patients. The bioavailability of subcutaneously administered epoetin delta is between 26% and 36%.

5.3 Preclinical safety data

Animal studies conducted with both Dynepo and epoetin alfa in pregnant female rats and rabbits did not show any teratogenic effect, but indicated class-related reversible effects on growth and haematopoiesis in the offspring.
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate monobasic, monohydrate
Sodium phosphate dibasic, heptahydrate
Polysorbate 20
Sodium chloride
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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 C – 8 C). Do not freeze. Keep the syringes in the outer carton to protect from light.

Unopened pre-filled syringes may be kept un-refrigerated but below 25°C for a single maximum period of 5 days. The revised expiry date for storage at below 25°C must not exceed the expiry date set in accordance with the 24 month shelf-life. Following 5 days storage at below 25°C the pre-filled syringes must be discarded.

6.5 Nature and contents of container

Prefilled Type I glass syringe with bromobutyl rubber stopper, 27 gauge stainless steel needle with rigid natural rubber and polystyrene needle shield, polystyrene plunger rod and a needle safety guard. Packs of 6 pre-filled syringes are available.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

When given subcutaneously, the site of injection should be rotated with each administration.

Inspect the pre-filled syringe before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency.
Do not shake the syringe. Prolonged vigorous shaking may denature the active substance.

The syringe is pre-assembled with a needle safety guard to prevent needle stick injury. This does not affect normal operation of the syringe and the syringe can be rotated in the device. When the injection has been administered the needle safety guard will cover the needle when releasing the plunger. Allow the syringe to move up until the entire needle is guarded.

7. MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/004

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 March 2002
Date of last renewal: 18 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 5,000 IU/0.5 ml solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled syringe containing 5,000 IU per 0.5 ml dose (10,000 IU/ml) of the active substance epoetin delta.
Epoetin delta is produced in human cells (HT-1080) by gene-activation technology.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe.

Clear, colourless and waterlike.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dynepo is indicated for the treatment of symptomatic anaemia associated with chronic renal failure(CRF) in adult patients. It may be used in patients on dialysis and in patients not on dialysis.

4.2 Posology and method of administration

Treatment with Dynepo should be initiated by physicians experienced in the treatment of anaemia associated with CRF.

The dosage of Dynepo must be adjusted individually to maintain the level of haemoglobin within the target range of 10 to 12g/dl.

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. Dynepo should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid puncture of peripheral veins.

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 (6.2 mmol/l) to 12g/dL (7.5mmol/l). A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12 g/dL (7.5mmol/l) are observed, are described below (see Dose Management section below).

A rise in haemoglobin of greater than 2 g/dL (1.25 mmol/l) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Patients should be monitored closely to ensure that the lowest approved dose of Dynepo is used to provide adequate control of the symptoms of anaemia.

Dose Management

Starting dose is 50 IU/kg three times a week if administered intravenously. 50 IU/kg twice a week if administered subcutaneously.

It may not be necessary to use erythropoietin during the first three months after starting peritoneal dialysis because an increase in haemoglobin often occurs during this period.

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of Dynepo before adjusting the dose. Because of the time required for erythropoiesis, an interval of approximately 4 weeks may occur between the time of a dose adjustment (initiation, increase, decrease or discontinuation) and a significant change in haemoglobin. In consequence, dose adjustment should not be made more frequently than once a month, unless clinically indicated.

Dose should be decreased by 25 % – 50 % or treatment temporarily withdrawn and then re-introduced with a lower dosage if:
- Haemoglobin reaches ≥ 12 g/dl or
- The rate of increase of haemoglobin > 2 g/dl in any 4 week period.

Dose should be increased by 25 % – 50 % if:
- Haemoglobin falls below < 10 g/dl and
- The rate of increase of haemoglobin is below 0.7 g/dl in any 4 week period.

Administration

Dynepo may be administered intravenously or subcutaneously. Subcutaneous self administration may be used after training by a medical professional.

The required weekly dose of Dynepo is lower when Dynepo is administered subcutaneously compared to intravenously.

For subcutaneous injection, the whole length of the needle should be inserted perpendicularly into a skin fold held between thumb and forefinger, the skin fold should be held throughout the injection.

Discard the syringe after initial single use.

Special populations

Dynepo is not indicated for the management of anaemia associated with cancer.

No special dosage adjustments are required in elderly patients.
Patients with homozygous sickle cell disease and renal failure should where possible be maintained at a total haemoglobin concentration between 7 and 9 g/dl.
The experience in children is limited.
Due to limited experience, the safety and efficacy of Dynepo could not be assessed in patients with impaired liver function.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients.
Uncontrolled hypertension.

4.4 Special warnings and precautions for use

In patients with chronic renal failure, 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 erythropoiesis stimulating agents (ESAs) were administered to target a haemoglobin of greater than 12 g/dL (7.5 mmol/l).

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

Hypertension

Most of patients with chronic renal failure have a history of hypertension. Patients on Dynepo therapy can experience increase in blood pressure or aggravation of existing hypertension.
Therefore, in patients treated with Dynepo, 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 like hypertensive encephalopathy and related complications (seizures, stroke). 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 anti-hypertensive medicines or dosing increase of existing anti-hypertensive medications. In addition, a reduction of the administered dose of Dynepo needs to be considered. If blood pressure values remain high, a transient interruption of Dynepo therapy may be required.
Once hypertension is controlled with more intensified therapy, Dynepo therapy should be re-started at a reduced dose.

Iron evaluation

During Dynepo therapy, absolute or functional iron deficiency may develop. This is the most common cause of an incomplete response to an erythropoietin therapy.
Therefore, prior to and during Dynepo therapy, the patient's iron stores, including transferrin saturation and serum ferritin, should be evaluated. Transferrin saturation should be at least 20 %, and ferritin should be at least 100 ng/ml. If transferrin saturation falls below 20 %, or if ferritin falls below 100 ng/ml, iron should be administered. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation and ferritin to levels that will adequately support erythropoiesis stimulated by Dynepo.
Anaemia in epoetin-resistant or hyporesponsive patients with failure to respond to 20,000 IU/week should be investigated, including referral to a haematologist.

In the iron-replete patient with an inadequate response to Dynepo therapy, the following conditions should be evaluated and treated, if appropriated:

- Infection/inflammation
- Occult blood loss
- Hyperparathyroidism/Osteitis fibrosa cystica
- Aluminium intoxication
- Haemoglobinopathies such as thalassaemia or sickle cell anaemia
- Vitamin deficiencies, i.e., folic acid or vitamin B12 deficiencies
- Haemolysis
- Malignant diseases including multiple myeloma and myelodysplastic syndrome
- Malnutrition

Laboratory monitoring

It is recommended that a complete blood count and platelet count is performed regularly.

The haemoglobin level should be determined once a week until it has stabilised in the suggested target range and the maintenance dose has been established. After any dose adjustment, the haemoglobin

should also be determined once weekly until it has stabilised in the target range. The haemoglobin level should then be monitored at regular intervals.

Serum chemistry values including creatinine and potassium should be monitored regularly during Dynepo therapy.

Other

Although it has not been observed with Dynepo, since anaphylactoid reactions may occur with erythropoietin, it is recommended that the first dose be administered under medical supervision.

The use of Dynepo in nephrosclerotic patients not yet undergoing dialysis should be defined individually, as a possible acceleration of progression of renal failure cannot be ruled out with certainty.

During haemodialysis, patients treated with Dynepo may require increased anticoagulation treatment to prevent clotting of the arterio-venous shunt.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

No interactions have been reported during treatment with Dynepo in the course of clinical trials.

4.6 Pregnancy and lactation

Pregnancy: Animal studies are insufficient with respect to effects on pregnancy (see section 5.3). The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women. In case of its use during pregnancy, concomitant iron substitution should be considered in the mother.
Lactation: It is not known whether Dynepo is excreted in human breast milk. Since many compounds are excreted in human milk, caution should be advised when Dynepo is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Approximately 10% of patients can be expected to experience an adverse drug reaction. The most common are hypertension, access related thrombosis and headache. Clinical experience with epoetins suggest hypertension and thrombosis risk may be reduced by titrating the dose to maintain haemoglobin levels between 10 to 12 g/dl.

The frequency of adverse events that were experienced during Dynepo therapy is tabulated below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Body System	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1000)
Blood and lymphatic system disorders:		Polycythaemia Thrombocytosis	
Nervous system disorders:	Headache		Convulsions
Vascular disorders:	Hypertension		
Gastrointestinal disorders:		Diarrhoea Nausea	
Skin and subcutaneous tissues disorders:		Pruritus	
General disorders and administration site conditions:	Access related thrombosis	Pain Injection site reaction (e.g. pain, haemorrhage) Flu-syndrome	

Increases in serum chemistry values including creatinine and potassium have been observed (see section 4.4).

4.9 Overdose

The maximum dose of epoetin delta that can be safely administered in single or multiple doses has not been determined.

Treatment can result in polycythaemia if the haemoglobin/haematocrit is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, treatment with epoetin delta should be temporarily withdrawn until the haemoglobin/haematocrit returns to the suggested target range. Epoetin delta can then be reintroduced with a lower dosage (see section 4.2).

If severe polycythaemia occurs, conventional methods (phlebotomy) may be indicated to decrease the haemoglobin level.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianaemic - ATC code: B03XA.

Erythropoietin is a glycoprotein that stimulates the formation of erythrocytes from precursors of the stem cell compartment. It acts as a mitosis stimulating factor and differentiation hormone.

The biological efficacy of erythropoietin has been demonstrated after intravenous and subcutaneous administration in various animal models in vivo (rats and dogs). After administration of epoetin delta, the number of erythrocytes, the Hb values and reticulocyte counts increase as well as the 59Fe-incorporation rate.

During the clinical trials, there were no indications of development of neutralising antibodies to epoetin delta in humans based on the clinical response.

When administration is halted, the eyrthropoietic parameters return toward baseline levels within the recovery period of 1-3 months. Subcutaneous administration results in a similar pattern of erythropoietic stimulation as after intravenous administration.

Patients with cancer

Dynepo is not indicated for the management of anaemia associated with cancer.

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 of epoetin alfa, beta and darbepoetin alfa involving a total of 2,833 patients, of which four were double-blind placebo-controlled studies and one was an open-label 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.

A systematic review has also been performed involving more than 9000 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 8167 patients). An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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. Survival outcomes and tumour progression in cancer patients that are being treated with Dynepo for anaemia associated with chronic renal failure have not been investigated. The extent to which the outcomes observed in the clinical studies discussed above may apply to this patient population is unclear, specifically considering that the dosages administered in the renal indication are lower than in the cancer indication..

5.2 Pharmacokinetic properties

The pharmacokinetics of erythropoietin following administration of epoetin delta has been examined in both healthy volunteers and patients with chronic renal failure. Following intravenous doses, volume of distribution approximates total blood volume and ranges from 0.063 to 0.097 l/kg. The elimination half-life ranges from 4.7 to 13.2 hours in patients. Half life is approximately 50% shorter in healthy subjects. Measurable concentrations of erythropoietin are maintained in the serum for at least 24 hours following doses ranging from 50 IU/kg to 300 IU/kg. Exposure to erythropoietin following administration of epoetin delta increases proportionately in patients given intravenous doses of 50 IU/kg to 300 IU/kg. No accumulation of epoetin delta was observed after repeated intravenous administration three times weekly.
Peak serum concentrations for subcutaneously administered epoetin delta occur between 8 and 36 hours following injection. The half-life of subcutaneously administered epoetin delta is prolonged compared to intravenous administration and ranges from 27 to 33 hours in patients. The bioavailability of subcutaneously administered epoetin delta is between 26% and 36%.

5.3 Preclinical safety data

Animal studies conducted with both Dynepo and epoetin alfa in pregnant female rats and rabbits did not show any teratogenic effect, but indicated class-related reversible effects on growth and haematopoiesis in the offspring.
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate monobasic, monohydrate
Sodium phosphate dibasic, heptahydrate
Polysorbate 20
Sodium chloride
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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 C – 8 C). Do not freeze. Keep the syringes in the outer carton to protect from light.

Unopened pre-filled syringes may be kept un-refrigerated but below 25°C for a single maximum period of 5 days. The revised expiry date for storage at below 25°C must not exceed the expiry date set in accordance with the 24 month shelf-life. Following 5 days storage at below 25°C the pre-filled syringes must be discarded.

6.5 Nature and contents of container

Prefilled Type I glass syringe with bromobutyl rubber stopper, 27 gauge stainless steel needle with rigid natural rubber and polystyrene needle shield, polystyrene plunger rod and a needle safety guard. Packs of 6 pre-filled syringes are available.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

When given subcutaneously, the site of injection should be rotated with each administration.

Inspect the pre-filled syringe before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency.
Do not shake the syringe. Prolonged vigorous shaking may denature the active substance.

The syringe is pre-assembled with a needle safety guard to prevent needle stick injury. This does not

affect normal operation of the syringe and the syringe can be rotated in the device. When the injection has been administered the needle safety guard will cover the needle when releasing the plunger. Allow the syringe to move up until the entire needle is guarded.

7. MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/010

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 March 2002
Date of last renewal: 18 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 6,000 IU/0.3 ml solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled syringe containing 6,000 IU per 0.3 ml dose (20,000 IU/ml) of the active substance epoetin delta.
Epoetin delta is produced in human cells (HT-1080) by gene-activation technology.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe.

Clear, colourless and waterlike.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dynepo is indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult patients. It may be used in patients on dialysis and in patients not on dialysis.

4.2 Posology and method of administration

Treatment with Dynepo should be initiated by physicians experienced in the treatment of anaemia associated with CRF.

The dosage of Dynepo must be adjusted individually to maintain the level of haemoglobin within the target range of 10 to 12g/dl.

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. Dynepo should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid puncture of peripheral veins.

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 (6.2 mmol/l) to 12g/dL (7.5mmol/l). A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12 g/dL (7.5mmol/l) are observed, are described below (see Dose Management section below).

A rise in haemoglobin of greater than 2 g/dL (1.25 mmol/l) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Patients should be monitored closely to ensure that the lowest approved dose of Dynepo is used to provide adequate control of the symptoms of anaemia.

Dose Management

Starting dose is 50 IU/kg three times a week if administered intravenously. 50 IU/kg twice a week if administered subcutaneously.

It may not be necessary to use erythropoietin during the first three months after starting peritoneal dialysis because an increase in haemoglobin often occurs during this period.

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of Dynepo before adjusting the dose. Because of the time required for erythropoiesis, an interval of approximately 4 weeks may occur between the time of a dose adjustment (initiation, increase, decrease or discontinuation) and a significant change in haemoglobin. In consequence, dose adjustment should not be made more frequently than once a month, unless clinically indicated.

Dose should be decreased by 25 % – 50 % or treatment temporarily withdrawn and then re-introduced with a lower dosage if:
- Haemoglobin reaches ≥ 12 g/dl or
- The rate of increase of haemoglobin > 2 g/dl in any 4 week period.

Dose should be increased by 25 % – 50 % if:
- Haemoglobin falls below < 10 g/dl and
- The rate of increase of haemoglobin is below 0.7 g/dl in any 4 week period.

Administration

Dynepo may be administered intravenously or subcutaneously. Subcutaneous self administration may be used after training by a medical professional.

The required weekly dose of Dynepo is lower when Dynepo is administered subcutaneously compared to intravenously.

For subcutaneous injection, the whole length of the needle should be inserted perpendicularly into a skin fold held between thumb and forefinger, the skin fold should be held throughout the injection.

Discard the syringe after initial single use.

Special populations

Dynepo is not indicated for the management of anaemia associated with cancer.

No special dosage adjustments are required in elderly patients.
Patients with homozygous sickle cell disease and renal failure should where possible be maintained at a total haemoglobin concentration between 7 and 9 g/dl.
The experience in children is limited.
Due to limited experience, the efficacy and safety of Dynepo could not be assessed in patients with impaired liver function.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients.
Uncontrolled hypertension.

4.4 Special warnings and precautions for use

In patients with chronic renal failure, 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 erythropoiesis stimulating agents (ESAs) were administered to target a haemoglobin of greater than 12 g/dL (7.5 mmol/l).

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

Hypertension

Most of patients with chronic renal failure have a history of hypertension. Patients on Dynepo therapy can experience increase in blood pressure or aggravation of existing hypertension.
Therefore, in patients treated with Dynepo, 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 like hypertensive encephalopathy and related complications (seizures, stroke). 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 anti-hypertensive medicines or dosing increase of existing anti-hypertensive medications. In addition, a reduction of the administered dose of Dynepo needs to be considered. If blood pressure values remain high, a transient interruption of Dynepo therapy may be required.
Once hypertension is controlled with more intensified therapy, Dynepo therapy should be re-started at a reduced dose.

Iron evaluation

During Dynepo therapy, absolute or functional iron deficiency may develop. This is the most common cause of an incomplete response to an erythropoietin therapy.
Therefore, prior to and during Dynepo therapy, the patient's iron stores, including transferrin saturation and serum ferritin, should be evaluated. Transferrin saturation should be at least 20 %, and ferritin should be at least 100 ng/ml. If transferrin saturation falls below 20 %, or if ferritin falls below 100 ng/ml, iron should be administered. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation and ferritin to levels that will adequately support erythropoiesis stimulated by Dynepo.
Anaemia in epoetin-resistant or hyporesponsive patients with failure to respond to 20,000 IU/week should be investigated, including referral to a haematologist.

In the iron-replete patient with an inadequate response to Dynepo therapy, the following conditions should be evaluated and treated, if appropriated:

- Infection/inflammation
- Occult blood loss
- Hyperparathyroidism/Osteitis fibrosa cystica
- Aluminium intoxication
- Haemoglobinopathies such as thalassaemia or sickle cell anaemia
- Vitamin deficiencies, i.e., folic acid or vitamin B12 deficiencies
- Haemolysis
- Malignant diseases including multiple myeloma and myelodysplastic syndrome
- Malnutrition

Laboratory monitoring

It is recommended that a complete blood count and platelet count is performed regularly.

The haemoglobin level should be determined once a week until it has stabilised in the suggested target range and the maintenance dose has been established. After any dose adjustment, the haemoglobin

should also be determined once weekly until it has stabilised in the target range. The haemoglobin level should then be monitored at regular intervals.

Serum chemistry values including creatinine and potassium should be monitored regularly during Dynepo therapy.

Other

Although it has not been observed with Dynepo, since anaphylactoid reactions may occur with erythropoietin, it is recommended that the first dose be administered under medical supervision.

The use of Dynepo in nephrosclerotic patients not yet undergoing dialysis should be defined individually, as a possible acceleration of progression of renal failure cannot be ruled out with certainty.

During haemodialysis, patients treated with Dynepo may require increased anticoagulation treatment to prevent clotting of the arterio-venous shunt.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

No interactions have been reported during treatment with Dynepo in the course of clinical trials.

4.6 Pregnancy and lactation

Pregnancy: Animal studies are insufficient with respect to effects on pregnancy (see section 5.3). The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women. In case of its use during pregnancy, concomitant iron substitution should be considered in the mother.
Lactation: It is not known whether Dynepo is excreted in human breast milk. Since many compounds are excreted in human milk, caution should be advised when Dynepo is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Approximately 10% of patients can be expected to experience an adverse drug reaction. The most common are hypertension, access related thrombosis and headache. Clinical experience with epoetins suggest hypertension and thrombosis risk may be reduced by titrating the dose to maintain haemoglobin levels between 10 to 12 g/dl.

The frequency of adverse events that were experienced during Dynepo therapy is tabulated below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Body System	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1000)
Blood and lymphatic system disorders:		Polycythaemia Thrombocytosis	
Nervous system disorders:	Headache		Convulsions
Vascular disorders:	Hypertension		
Gastrointestinal disorders:		Diarrhoea Nausea	
Skin and subcutaneous tissues disorders:		Pruritus	
General disorders and administration site conditions:	Access related thrombosis	Pain Injection site reaction (e.g. pain, haemorrhage) Flu-syndrome	

Increases in serum chemistry values including creatinine and potassium have been observed (see section 4.4).

4.9 Overdose

The maximum dose of epoetin delta that can be safely administered in single or multiple doses has not been determined.

Treatment can result in polycythaemia if the haemoglobin/haematocrit is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, treatment with epoetin delta should be temporarily withdrawn until the haemoglobin/haematocrit returns to the suggested target range. Epoetin delta can then be reintroduced with a lower dosage (see section 4.2).

If severe polycythaemia occurs, conventional methods (phlebotomy) may be indicated to decrease the haemoglobin level.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianaemic - ATC code: B03XA.

Erythropoietin is a glycoprotein that stimulates the formation of erythrocytes from precursors of the stem cell compartment. It acts as a mitosis stimulating factor and differentiation hormone.

The biological efficacy of erythropoietin has been demonstrated after intravenous and subcutaneous administration in various animal models in vivo (rats and dogs). After administration of epoetin delta, the number of erythrocytes, the Hb values and reticulocyte counts increase as well as the 59Fe-incorporation rate.

During the clinical trials, there were no indications of development of neutralising antibodies to epoetin delta in humans based on the clinical response.

When administration is halted, the eyrthropoietic parameters return toward baseline levels within the recovery period of 1-3 months. Subcutaneous administration results in a similar pattern of erythropoietic stimulation as after intravenous administration.

Patients with cancer

Dynepo is not indicated for the management of anaemia associated with cancer.

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 of epoetin alfa, beta and darbepoetin alfa involving a total of 2,833 patients, of which four were double-blind placebo-controlled studies and one was an open-label 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.

A systematic review has also been performed involving more than 9000 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 8167 patients). An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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. Survival outcomes and tumour progression in cancer patients that are being treated with Dynepo for anaemia associated with chronic renal failure have not been investigated. The extent to which the outcomes observed in the clinical studies discussed above may apply to this patient population is unclear, specifically considering that the dosages administered in the renal indication are lower than in the cancer indication.

5.2 Pharmacokinetic properties

The pharmacokinetics of erythropoietin following administration of epoetin delta has been examined in both healthy volunteers and patients with chronic renal failure. Following intravenous doses, volume of distribution approximates total blood volume and ranges from 0.063 to 0.097 l/kg. The elimination half-life ranges from 4.7 to 13.2 hours in patients. Half life is approximately 50% shorter in healthy subjects. Measurable concentrations of erythropoietin are maintained in the serum for at least 24 hours following doses ranging from 50 IU/kg to 300 IU/kg. Exposure to erythropoietin following administration of epoetin delta increases proportionately in patients given intravenous doses of 50 IU/kg to 300 IU/kg. No accumulation of epoetin delta was observed after repeated intravenous administration three times weekly.
Peak serum concentrations for subcutaneously administered epoetin delta occur between 8 and 36 hours following injection. The half-life of subcutaneously administered epoetin delta is prolonged compared to intravenous administration and ranges from 27 to 33 hours in patients. The bioavailability of subcutaneously administered epoetin delta is between 26% and 36%.

5.3 Preclinical safety data

Animal studies conducted with both Dynepo and epoetin alfa in pregnant female rats and rabbits did not show any teratogenic effect, but indicated class-related reversible effects on growth and haematopoiesis in the offspring.
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate monobasic, monohydrate
Sodium phosphate dibasic, heptahydrate
Polysorbate 20
Sodium chloride
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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 C – 8 C). Do not freeze. Keep the syringes in the outer carton to protect from light.

Unopened pre-filled syringes may be kept un-refrigerated but below 25°C for a single maximum period of 5 days. The revised expiry date for storage at below 25°C must not exceed the expiry date set in accordance with the 24 month shelf-life. Following 5 days storage at below 25°C the pre-filled syringes must be discarded.

6.5 Nature and contents of container

Prefilled Type I glass syringe with bromobutyl rubber stopper, 27 gauge stainless steel needle with rigid natural rubber and polystyrene needle shield, polystyrene plunger rod and a needle safety guard. Packs of 6 pre-filled syringes are available.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

When given subcutaneously, the site of injection should be rotated with each administration.

Inspect the pre-filled syringe before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency.
Do not shake the syringe. Prolonged vigorous shaking may denature the active substance.

The syringe is pre-assembled with a needle safety guard to prevent needle stick injury. This does not affect normal operation of the syringe and the syringe can be rotated in the device. When the injection

has been administered the needle safety guard will cover the needle when releasing the plunger. Allow the syringe to move up until the entire needle is guarded.

7. MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/011

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 March 2002
Date of last renewal: 18 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 8,000 IU/0.4 ml solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled syringe containing 8,000 IU per 0.4 ml dose (20,000 IU/ml) of the active substance epoetin delta.
Epoetin delta is produced in human cells (HT-1080) by gene-activation technology.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe.
Clear, colourless and waterlike.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dynepo is indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult patients. It may be used in patients on dialysis and in patients not on dialysis.

4.2 Posology and method of administration

Treatment with Dynepo should be initiated by physicians experienced in the treatment of anaemia associated with CRF.

The dosage of Dynepo must be adjusted individually to maintain the level of haemoglobin within the target range of 10 to 12g/dl.

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. Dynepo should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid puncture of peripheral veins.

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 (6.2 mmol/l) to 12g/dL (7.5mmol/l). A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12 g/dL (7.5mmol/l) are observed, are described below (see Dose Management section below).

A rise in haemoglobin of greater than 2 g/dL (1.25 mmol/l) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Patients should be monitored closely to ensure that the lowest approved dose of Dynepo is used to provide adequate control of the symptoms of anaemia.

Dose Management

Starting dose is 50 IU/kg three times a week if administered intravenously. 50 IU/kg twice a week if administered subcutaneously.

It may not be necessary to use erythropoietin during the first three months after starting peritoneal dialysis because an increase in haemoglobin often occurs during this period.

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of Dynepo before adjusting the dose. Because of the time required for erythropoiesis, an interval of approximately 4 weeks may occur between the time of a dose adjustment (initiation, increase, decrease or discontinuation) and a significant change in haemoglobin. In consequence, dose adjustment should not be made more frequently than once a month, unless clinically indicated.

Dose should be decreased by 25 % – 50 % or treatment temporarily withdrawn and then re-introduced with a lower dosage if:
- Haemoglobin reaches ≥ 12 g/dl or
- The rate of increase of haemoglobin > 2 g/dl in any 4 week period.

Dose should be increased by 25 % – 50 % if:
- Haemoglobin falls below < 10 g/dl and
- The rate of increase of haemoglobin is below 0.7 g/dl in any 4 week period.

Administration

Dynepo may be administered intravenously or subcutaneously. Subcutaneous self administration may be used after training by a medical professional.

The required weekly dose of Dynepo is lower when Dynepo is administered subcutaneously compared to intravenously.

For subcutaneous injection, the whole length of the needle should be inserted perpendicularly into a skin fold held between thumb and forefinger, the skin fold should be held throughout the injection.

Discard the syringe after initial single use.

Special populations

Dynepo is not indicated for the management of anaemia associated with cancer.

No special dosage adjustments are required in elderly patients.
Patients with homozygous sickle cell disease and renal failure should where possible be maintained at a total haemoglobin concentration between 7 and 9 g/dl.
The experience in children is limited.
Due to limited experience, the efficacy and safety of Dynepo could not be assessed in patients with impaired liver function.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients.
Uncontrolled hypertension.

4.4 Special warnings and precautions for use

In patients with chronic renal failure, 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 erythropoiesis stimulating agents (ESAs) were administered to target a haemoglobin of greater than 12 g/dL (7.5 mmol/l).

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

Hypertension

Most of patients with chronic renal failure have a history of hypertension. Patients on Dynepo therapy can experience increase in blood pressure or aggravation of existing hypertension.
Therefore, in patients treated with Dynepo, 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 like hypertensive encephalopathy and related complications (seizures, stroke). 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 anti-hypertensive medicines or dosing increase of existing anti-hypertensive medications. In addition, a reduction of the administered dose of Dynepo needs to be considered. If blood pressure values remain high, a transient interruption of Dynepo therapy may be required.
Once hypertension is controlled with more intensified therapy, Dynepo therapy should be re-started at a reduced dose.

Iron evaluation

During Dynepo therapy, absolute or functional iron deficiency may develop. This is the most common cause of an incomplete response to an erythropoietin therapy.
Therefore, prior to and during Dynepo therapy, the patient's iron stores, including transferrin saturation and serum ferritin, should be evaluated. Transferrin saturation should be at least 20 %, and ferritin should be at least 100 ng/ml. If transferrin saturation falls below 20 %, or if ferritin falls below 100 ng/ml, iron should be administered. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation and ferritin to levels that will adequately support erythropoiesis stimulated by Dynepo.
Anaemia in epoetin-resistant or hyporesponsive patients with failure to respond to 20,000 IU/week should be investigated, including referral to a haematologist.

In the iron-replete patient with an inadequate response to Dynepo therapy, the following conditions should be evaluated and treated, if appropriated:

- Infection/inflammation
- Occult blood loss
- Hyperparathyroidism/Osteitis fibrosa cystica
- Aluminium intoxication
- Haemoglobinopathies such as thalassaemia or sickle cell anaemia
- Vitamin deficiencies, i.e., folic acid or vitamin B12 deficiencies
- Haemolysis
- Malignant diseases including multiple myeloma and myelodysplastic syndrome
- Malnutrition

Laboratory monitoring

It is recommended that a complete blood count and platelet count is performed regularly.

The haemoglobin level should be determined once a week until it has stabilised in the suggested target range and the maintenance dose has been established. After any dose adjustment, the haemoglobin should also be determined once weekly until it has stabilised in the target range. The haemoglobin level should then be monitored at regular intervals.

Serum chemistry values including creatinine and potassium should be monitored regularly during Dynepo therapy.

Other

Although it has not been observed with Dynepo, since anaphylactoid reactions may occur with erythropoietin, it is recommended that the first dose be administered under medical supervision.

The use of Dynepo in nephrosclerotic patients not yet undergoing dialysis should be defined individually, as a possible acceleration of progression of renal failure cannot be ruled out with certainty.

During haemodialysis, patients treated with Dynepo may require increased anticoagulation treatment to prevent clotting of the arterio-venous shunt.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

No interactions have been reported during treatment with Dynepo in the course of clinical trials.

4.6 Pregnancy and lactation

Pregnancy: Animal studies are insufficient with respect to effects on pregnancy (see section 5.3). The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women. In case of its use during pregnancy, concomitant iron substitution should be considered in the mother.
Lactation: It is not known whether Dynepo is excreted in human breast milk. Since many compounds are excreted in human milk, caution should be advised when Dynepo is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Approximately 10% of patients can be expected to experience an adverse drug reaction. The most common are hypertension, access related thrombosis and headache. Clinical experience with epoetins suggest hypertension and thrombosis risk may be reduced by titrating the dose to maintain haemoglobin levels between 10 to 12 g/dl.

The frequency of adverse events that were experienced during Dynepo therapy is tabulated below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Body System	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1000)
Blood and lymphatic system disorders:		Polycythaemia Thrombocytosis	
Nervous system disorders:	Headache		Convulsions
Vascular disorders:	Hypertension		
Gastrointestinal disorders:		Diarrhoea Nausea	
Skin and subcutaneous tissues disorders:		Pruritus	
General disorders and administration site conditions:	Access related thrombosis	Pain Injection site reaction (e.g. pain, haemorrhage) Flu-syndrome	

Increases in serum chemistry values including creatinine and potassium have been observed (see section 4.4).

4.9 Overdose

The maximum dose of epoetin delta that can be safely administered in single or multiple doses has not been determined.

Treatment can result in polycythaemia if the haemoglobin/haematocrit is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, treatment with epoetin delta should be temporarily withdrawn until the haemoglobin/haematocrit returns to the suggested target range. Epoetin delta can then be reintroduced with a lower dosage (see section 4.2).

If severe polycythaemia occurs, conventional methods (phlebotomy) may be indicated to decrease the haemoglobin level.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianaemic - ATC code: B03XA.

Erythropoietin is a glycoprotein that stimulates the formation of erythrocytes from precursors of the stem cell compartment. It acts as a mitosis stimulating factor and differentiation hormone.

The biological efficacy of erythropoietin has been demonstrated after intravenous and subcutaneous administration in various animal models in vivo (rats and dogs). After administration of epoetin delta, the number of erythrocytes, the Hb values and reticulocyte counts increase as well as the 59Fe-incorporation rate.

During the clinical trials, there were no indications of development of neutralising antibodies to epoetin delta in humans based on the clinical response.

When administration is halted, the eyrthropoietic parameters return toward baseline levels within the recovery period of 1-3 months. Subcutaneous administration results in a similar pattern of erythropoietic stimulation as after intravenous administration.

Patients with cancer

Dynepo is not indicated for the management of anaemia associated with cancer.

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 of epoetin alfa, beta and darbepoetin alfa involving a total of 2,833 patients, of which four were double-blind placebo-controlled studies and one was an open-label 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.

A systematic review has also been performed involving more than 9000 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 8167 patients). An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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. Survival outcomes and tumour progression in cancer patients that are being treated with Dynepo for anaemia associated with chronic renal failure have not been investigated. The extent to which the outcomes observed in the clinical studies discussed above may apply to this patient population is unclear, specifically considering that the dosages administered in the renal indication are lower than in the cancer indication.

5.2 Pharmacokinetic properties

The pharmacokinetics of erythropoietin following administration of epoetin delta has been examined in both healthy volunteers and patients with chronic renal failure. Following intravenous doses, volume of distribution approximates total blood volume and ranges from 0.063 to 0.097 l/kg. The elimination half-life ranges from 4.7 to 13.2 hours in patients. Half life is approximately 50% shorter in healthy subjects. Measurable concentrations of erythropoietin are maintained in the serum for at least 24 hours following doses ranging from 50 IU/kg to 300 IU/kg. Exposure to erythropoietin following administration of epoetin delta increases proportionately in patients given intravenous doses of 50 IU/kg to 300 IU/kg. No accumulation of epoetin delta was observed after repeated intravenous administration three times weekly.
Peak serum concentrations for subcutaneously administered epoetin delta occur between 8 and 36 hours following injection. The half-life of subcutaneously administered epoetin delta is prolonged compared to intravenous administration and ranges from 27 to 33 hours in patients. The

bioavailability of subcutaneously administered epoetin delta is between 26% and 36%.

5.3 Preclinical safety data

Animal studies conducted with both Dynepo and epoetin alfa in pregnant female rats and rabbits did not show any teratogenic effect, but indicated class-related reversible effects on growth and haematopoiesis in the offspring.
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate monobasic, monohydrate
Sodium phosphate dibasic, heptahydrate
Polysorbate 20
Sodium chloride
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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 C – 8 C). Do not freeze. Keep the syringes in the outer carton to protect from light.

Unopened pre-filled syringes may be kept un-refrigerated but below 25°C for a single maximum period of 5 days. The revised expiry date for storage at below 25°C must not exceed the expiry date set in accordance with the 24 month shelf-life. Following 5 days storage at below 25°C the pre-filled syringes must be discarded.

6.5 Nature and contents of container

Prefilled Type I glass syringe with bromobutyl rubber stopper, 27 gauge stainless steel needle with rigid natural rubber and polystyrene needle shield, polystyrene plunger rod and a needle safety guard. Packs of 6 pre-filled syringes are available.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

When given subcutaneously, the site of injection should be rotated with each administration.

Inspect the pre-filled syringe before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency.

Do not shake the syringe. Prolonged vigorous shaking may denature the active substance.

The syringe is pre-assembled with a needle safety guard to prevent needle stick injury. This does not affect normal operation of the syringe and the syringe can be rotated in the device. When the injection has been administered the needle safety guard will cover the needle when releasing the plunger. Allow the syringe to move up until the entire needle is guarded.

7. MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/012

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 March 2002
Date of last renewal: 18 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 10,000 IU/0.5 ml solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled syringe containing 10,000 IU per 0.5 ml dose (20,000 IU/ml) of the active substance epoetin delta.
Epoetin delta is produced in human cells (HT-1080) by gene-activation technology.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe.
Clear, colourless and waterlike.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dynepo is indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult patients. It may be used in patients on dialysis and in patients not on dialysis.

4.2 Posology and method of administration

Treatment with Dynepo should be initiated by physicians experienced in the treatment of anaemia associated with CRF.

The dosage of Dynepo must be adjusted individually to maintain the level of haemoglobin within the target range of 10 to 12g/dl.

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. Dynepo should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid puncture of peripheral veins.

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 (6.2 mmol/l) to 12g/dL (7.5mmol/l). A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12 g/dL (7.5mmol/l) are observed, are described below (see Dose Management section below).

A rise in haemoglobin of greater than 2 g/dL (1.25 mmol/l) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Patients should be monitored closely to ensure that the lowest approved dose of Dynepo is used to provide adequate control of the symptoms of anaemia.

Dose Management

Starting dose is 50 IU/kg three times a week if administered intravenously. 50 IU/kg twice a week if administered subcutaneously.

It may not be necessary to use erythropoietin during the first three months after starting peritoneal dialysis because an increase in haemoglobin often occurs during this period.

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of Dynepo before adjusting the dose. Because of the time required for erythropoiesis, an interval of approximately 4 weeks may occur between the time of a dose adjustment (initiation, increase, decrease or discontinuation) and a significant change in haemoglobin. In consequence, dose adjustment should not be made more frequently than once a month, unless clinically indicated.

Dose should be decreased by 25 % – 50 % or treatment temporarily withdrawn and then re-introduced with a lower dosage if:
- Haemoglobin reaches ≥ 12 g/dl or
- The rate of increase of haemoglobin > 2 g/dl in any 4 week period.

Dose should be increased by 25 % – 50 % if:
- Haemoglobin falls below < 10 g/dl and
- The rate of increase of haemoglobin is below 0.7 g/dl in any 4 week period.

Administration

Dynepo may be administered intravenously or subcutaneously. Subcutaneous self administration may be used after training by a medical professional.

The required weekly dose of Dynepo is lower when Dynepo is administered subcutaneously compared to intravenously.

For subcutaneous injection, the whole length of the needle should be inserted perpendicularly into a skin fold held between thumb and forefinger, the skin fold should be held throughout the injection.

Discard the syringe after initial single use.

Special populations

Dynepo is not indicated for the management of anaemia associated with cancer.

No special dosage adjustments are required in elderly patients.
Patients with homozygous sickle cell disease and renal failure should where possible be maintained at a total haemoglobin concentration between 7 and 9 g/dl.
The experience in children is limited
Due to limited experience, the safety and efficacy of Dynepo could not be assessed in patients with impaired liver function.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients.
Uncontrolled hypertension.

4.4 Special warnings and precautions for use

In patients with chronic renal failure, 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 erythropoiesis stimulating agents (ESAs) were administered to target a haemoglobin of greater than 12 g/dL (7.5 mmol/l).

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

Hypertension

Most of patients with chronic renal failure have a history of hypertension. Patients on Dynepo therapy can experience increase in blood pressure or aggravation of existing hypertension.
Therefore, in patients treated with Dynepo, 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 like hypertensive encephalopathy and related complications (seizures, stroke). 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 anti-hypertensive medicines or dosing increase of existing anti-hypertensive medications. In addition, a reduction of the administered dose of Dynepo needs to be considered. If blood pressure values remain high, a transient interruption of Dynepo therapy may be required.
Once hypertension is controlled with more intensified therapy, Dynepo therapy should be re-started at a reduced dose.

Iron evaluation

During Dynepo therapy, absolute or functional iron deficiency may develop. This is the most common cause of an incomplete response to an erythropoietin therapy.
Therefore, prior to and during Dynepo therapy, the patient's iron stores, including transferrin saturation and serum ferritin, should be evaluated. Transferrin saturation should be at least 20 %, and ferritin should be at least 100 ng/ml. If transferrin saturation falls below 20 %, or if ferritin falls below 100 ng/ml, iron should be administered. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation and ferritin to levels that will adequately support erythropoiesis stimulated by Dynepo.
Anaemia in epoetin-resistant or hyporesponsive patients with failure to respond to 20,000 IU/week should be investigated, including referral to a haematologist.

In the iron-replete patient with an inadequate response to Dynepo therapy, the following conditions should be evaluated and treated, if appropriated:

- Infection/inflammation
- Occult blood loss
- Hyperparathyroidism/Osteitis fibrosa cystica
- Aluminium intoxication
- Haemoglobinopathies such as thalassaemia or sickle cell anaemia
- Vitamin deficiencies, i.e., folic acid or vitamin B12 deficiencies
- Haemolysis
- Malignant diseases including multiple myeloma and myelodysplastic syndrome
- Malnutrition

Laboratory monitoring

It is recommended that a complete blood count and platelet count is performed regularly.

The haemoglobin level should be determined once a week until it has stabilised in the suggested target range and the maintenance dose has been established. After any dose adjustment, the haemoglobin should also be determined once weekly until it has stabilised in the target range. The haemoglobin level should then be monitored at regular intervals.

Serum chemistry values including creatinine and potassium should be monitored regularly during Dynepo therapy.

Other

Although it has not been observed with Dynepo, since anaphylactoid reactions may occur with erythropoietin, it is recommended that the first dose be administered under medical supervision.

The use of Dynepo in nephrosclerotic patients not yet undergoing dialysis should be defined individually, as a possible acceleration of progression of renal failure cannot be ruled out with certainty.

During haemodialysis, patients treated with Dynepo may require increased anticoagulation treatment to prevent clotting of the arterio-venous shunt.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

No interactions have been reported during treatment with Dynepo in the course of clinical trials.

4.6 Pregnancy and lactation

Pregnancy: Animal studies are insufficient with respect to effects on pregnancy (see section 5.3). The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women. In case of its use during pregnancy, concomitant iron substitution should be considered in the mother.
Lactation: It is not known whether Dynepo is excreted in human breast milk. Since many compounds are excreted in human milk, caution should be advised when Dynepo is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Approximately 10% of patients can be expected to experience an adverse drug reaction. The most common are hypertension, access related thrombosis and headache. Clinical experience with epoetins suggest hypertension and thrombosis risk may be reduced by titrating the dose to maintain haemoglobin levels between 10 to 12 g/dl.

The frequency of adverse events that were experienced during Dynepo therapy is tabulated below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Body System	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1000)
Blood and lymphatic system disorders:		Polycythaemia Thrombocytosis	
Nervous system disorders:	Headache		Convulsions
Vascular disorders:	Hypertension		
Gastrointestinal disorders:		Diarrhoea Nausea	
Skin and subcutaneous tissues disorders:		Pruritus	
General disorders and administration site conditions:	Access related thrombosis	Pain Injection site reaction (e.g. pain, haemorrhage) Flu-syndrome	

Increases in serum chemistry values including creatinine and potassium have been observed (see section 4.4).

4.9 Overdose

The maximum dose of epoetin delta that can be safely administered in single or multiple doses has not been determined.

Treatment can result in polycythaemia if the haemoglobin/haematocrit is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, treatment with epoetin delta should be temporarily withdrawn until the haemoglobin/haematocrit returns to the suggested target range. Epoetin delta can then be reintroduced with a lower dosage (see section 4.2).

If severe polycythaemia occurs, conventional methods (phlebotomy) may be indicated to decrease the haemoglobin level.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianaemic - ATC code: B03XA.
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Erythropoietin is a glycoprotein that stimulates the formation of erythrocytes from precursors of the stem cell compartment. It acts as a mitosis stimulating factor and differentiation hormone.

The biological efficacy of erythropoietin has been demonstrated after intravenous and subcutaneous administration in various animal models in vivo (rats and dogs). After administration of epoetin delta, the number of erythrocytes, the Hb values and reticulocyte counts increase as well as the 59Fe-incorporation rate.

During the clinical trials, there were no indications of development of neutralising antibodies to epoetin delta in humans based on the clinical response.

When administration is halted, the eyrthropoietic parameters return toward baseline levels within the recovery period of 1-3 months. Subcutaneous administration results in a similar pattern of erythropoietic stimulation as after intravenous administration.

Patients with cancer

Dynepo is not indicated for the management of anaemia associated with cancer.

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 of epoetin alfa, beta and darbepoetin alfa involving a total of 2,833 patients, of which four were double-blind placebo-controlled studies and one was an open-label 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.

A systematic review has also been performed involving more than 9000 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 8167 patients). An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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. Survival outcomes and tumour progression in cancer patients that are being treated with Dynepo for anaemia associated with chronic renal failure have not been investigated. The extent to which the outcomes observed in the clinical studies discussed above may apply to this patient population is unclear, specifically considering that the dosages administered in the renal indication are lower than in the cancer indication.

5.2 Pharmacokinetic properties

The pharmacokinetics of erythropoietin following administration of epoetin delta has been examined in both healthy volunteers and patients with chronic renal failure. Following intravenous doses, volume of distribution approximates total blood volume and ranges from 0.063 to 0.097 l/kg. The elimination half-life ranges from 4.7 to 13.2 hours in patients. Half life is approximately 50% shorter in healthy subjects. Measurable concentrations of erythropoietin are maintained in the serum for at least 24 hours following doses ranging from 50 IU/kg to 300 IU/kg. Exposure to erythropoietin following administration of epoetin delta increases proportionately in patients given intravenous doses of 50 IU/kg to 300 IU/kg. No accumulation of epoetin delta was observed after repeated intravenous administration three times weekly.
Peak serum concentrations for subcutaneously administered epoetin delta occur between 8 and 36 hours following injection. The half-life of subcutaneously administered epoetin delta is prolonged compared to intravenous administration and ranges from 27 to 33 hours in patients. The bioavailability of subcutaneously administered epoetin delta is between 26% and 36%.

5.3 Preclinical safety data

Animal studies conducted with both Dynepo and epoetin alfa in pregnant female rats and rabbits did not show any teratogenic effect, but indicated class-related reversible effects on growth and haematopoiesis in the offspring.
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate monobasic, monohydrate
Sodium phosphate dibasic, heptahydrate
Polysorbate 20
Sodium chloride
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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 C – 8 C). Do not freeze. Keep the syringes in the outer carton to protect from light.

Unopened pre-filled syringes may be kept un-refrigerated but below 25°C for a single maximum period of 5 days. The revised expiry date for storage at below 25°C must not exceed the expiry date set in accordance with the 24 month shelf-life. Following 5 days storage at below 25°C the pre-filled syringes must be discarded.

6.5 Nature and contents of container

Prefilled Type I glass syringe with bromobutyl rubber stopper, 27 gauge stainless steel needle with rigid natural rubber and polystyrene needle shield, polystyrene plunger rod and a needle safety guard. Packs of 6 pre-filled syringes are available.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

When given subcutaneously, the site of injection should be rotated with each administration.

Inspect the pre-filled syringe before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency.
Do not shake the syringe. Prolonged vigorous shaking may denature the active substance.

The syringe is pre-assembled with a needle safety guard to prevent needle stick injury. This does not affect normal operation of the syringe and the syringe can be rotated in the device. When the injection has been administered the needle safety guard will cover the needle when releasing the plunger. Allow the syringe to move up until the entire needle is guarded.

7. MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/005

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 March 2002
Date of last renewal: 18 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Lonza Biologics, plc
228 Bath Road
Slough
Berkshire SL1 4DX
United Kingdom

Name and address of the manufacturer responsible for batch release

Shire Human Genetic Therapies AB
Åldermansgatan 2
P.O. Box 1117
SE-221 04 Lund
Sweden

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

- **OTHER CONDITIONS**

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan.

An updated Risk Management Plan should be provided as per CHMP Guideline on Risk Management Systems for medicinal products for human use except that routine updates of the Risk Management Plan should be provided yearly until the start of the three-yearly PSUR cycle.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 1,000 IU/0.5 ml solution for injection in a prefilled syringe
Epoetin delta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Pre-filled syringe containing 1,000 IU per 0.5 ml dose (2,000 IU/ml) of the active substance epoetin delta.

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, polysorbate 20 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, 0.5ml of epoetin delta in a pre-filled syringe: pack size of 6

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Intravenous or subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions. Read package leaflet before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator ($2^{o}C – 8^{o}C$)
Do not freeze. Keep syringes in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only. Do not use any remaining liquid.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/001

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dynepo 1000

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 1,000 IU/0.5ml
Injection
Epoetin delta

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Dynepo 1,000 IU/0.5 ml
injection
Epoetin delta
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml (2,000 IU/ml)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 2,000 IU/0.5 ml solution for injection in a prefilled syringe
Epoetin delta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Pre-filled syringe containing 2,000 IU per 0.5 ml dose (4,000 IU/ml) of the active substance epoetin delta.

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, polysorbate 20 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, 0.5ml of epoetin delta in a pre-filled syringe: pack size of 6

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Intravenous or subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions. Read package leaflet before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator ($2^{o}C – 8^{o}C$)
Do not freeze. Keep syringes in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only. Do not use any remaining liquid.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/002

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dynepo 2000

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 2,000 IU/0.5ml
Injection
Epoetin delta

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Dynepo 2,000 IU/0.5 ml
injection
Epoetin delta
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml (4,000 IU/ml)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 3,000 IU/0.3 ml solution for injection in a prefilled syringe
Epoetin delta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Pre-filled syringe containing 3,000 IU per 0.3 ml dose (10,000 IU/ml) of the active substance epoetin delta.

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, polysorbate 20 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, 0.3ml of epoetin delta in a pre-filled syringe: pack size of 6

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Intravenous or subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions. Read package leaflet before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator ($2^{o}C – 8^{o}C$)
Do not freeze. Keep syringes in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only. Do not use any remaining liquid.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/003

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dynepo 3000

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 3,000 IU/0.3ml
Injection
Epoetin delta

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Dynepo 3,000 IU/0.3 ml
injection
Epoetin delta
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.3 ml.(10,000 IU/ml)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 4,000 IU/0.4 ml solution for injection in a prefilled syringe
Epoetin delta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Pre-filled syringe containing 4,000 IU per 0.4 ml dose (10,000 IU/ml) of the active substance epoetin delta.

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, polysorbate 20 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, 0.4ml of epoetin delta in a pre-filled syringe: pack size of 6

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Intravenous or subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions. Read package leaflet before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator ($2^{o}C – 8^{o}C$)
Do not freeze. Keep syringes in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only. Do not use any remaining liquid.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/004

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dynepo 4000

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 4,000 IU/0.4ml
Injection
Epoetin delta

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Dynepo 4,000 IU/0.4 ml
injection
Epoetin delta
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml.(10,000 IU/ml°)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 5,000 IU/0.5 ml solution for injection in a prefilled syringe
Epoetin delta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Pre-filled syringe containing 5,000 IU per 0.5 ml dose (10,000 IU/ml) of the active substance epoetin delta

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, polysorbate 20 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, 0.5ml of epoetin delta in a pre-filled syringe: pack size of 6

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Intravenous or subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions. Read package leaflet before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator ($2^{o}C – 8^{o}C$)
Do not freeze. Keep syringes in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only. Do not use any remaining liquid.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/010

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dynepo 5000

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 5,000 IU/0.5ml
Injection
Epoetin delta

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Dynepo 5,000 IU/0.5 ml
injection
Epoetin delta
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml (10,000 IU/ml)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 6,000 IU/0.3 ml solution for injection in a prefilled syringe
Epoetin delta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Pre-filled syringe containing 6,000 IU per 0.3 ml dose (20,000 IU/ml) of the active substance epoetin delta.

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, polysorbate 20 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, 0.3ml of epoetin delta in a pre-filled syringe: pack size of 6

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Intravenous or subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions. Read package leaflet before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator ($2^{o}C – 8^{o}C$)
Do not freeze. Keep syringes in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only. Do not use any remaining liquid.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/011

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dynepo 6000

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 6,000 IU/0.3ml
Injection
Epoetin delta

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Dynepo 6,000 IU/0.3 ml
injection
Epoetin delta
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.3 ml (20,000 IU/ml)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 8,000 IU/0.4 ml solution for injection in a prefilled syringe
Epoetin delta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Pre-filled syringe containing 8,000 IU per 0.4 ml dose (20,000 IU/ml) of the active substance epoetin delta.

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, polysorbate 20 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, 0.4ml of epoetin delta in a pre-filled syringe: pack size of 6

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Intravenous or subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions. Read package leaflet before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator ($2^{o}C – 8^{o}C$)
Do not freeze. Keep syringes in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only. Do not use any remaining liquid.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/012

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dynepo 8000

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 8,000 IU/0.4ml
Injection
Epoetin delta

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Dynepo 8,000 IU/0.4 ml
injection
Epoetin delta
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml (20,000 IU/ml)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 10,000 IU/0.5 ml solution for injection in a prefilled syringe
Epoetin delta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Pre-filled syringe containing 10,000 IU per 0.5 ml dose (20,000 IU/ml) of the active substance epoetin delta.

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, polysorbate 20 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, 0.5ml of epoetin delta in a pre-filled syringe: pack size of 6

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Intravenous or subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions. Read package leaflet before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator ($2^{o}C$ – $8^{o}C$)
Do not freeze. Keep syringes in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only. Do not use any remaining liquid.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham, Basingstoke
Hampshire, RG24 8EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/211/005

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dynepo 10000

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Dynepo 10,000 IU/0.5ml
Injection
Epoetin delta

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Dynepo 10,000 IU/0.5 ml
injection
Epoetin delta
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml (20,000 IU/ml)

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET – INFORMATION FOR THE USER

Dynepo 1,000 IU/0.5 ml solution for injection in a pre-filled syringe
Dynepo 2,000 IU/0.5ml solution for injection in a pre-filled syringe
Dynepo 3,000 IU/0.3ml solution for injection in a pre-filled syringe
Dynepo 4,000 IU/0.4ml solution for injection in a pre-filled syringe
Dynepo 5,000 IU/0.5 ml solution for injection in a pre-filled syringe
Dynepo 6,000 IU/0.3 ml solution for injection in a pre-filled syringe
Dynepo 8,000 IU/0.4 ml solution for injection in a pre-filled syringe
Dynepo 10,000 IU/0.5ml solution for injection in a pre-filled syringe
Epoetin delta

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Dynepo is and what it is used for
2. Before you take Dynepo
3. How to take Dynepo
4. Possible side effects
5. How to store Dynepo
6. Further information

1. WHAT DYNEPO IS AND WHAT IT IS USED FOR

Epoetin delta is a human erythropoietin made by a technology process called gene-activation, which uses a human cell line.
Epoetin delta is a hormone which stimulates the production of red blood cells in the bone marrow. Red blood cells are very important since they contain haemoglobin, a protein which distributes oxygen in your body.

Dynepo is used for treating the symptoms of anaemia (which include tiredness, weakness and shortness of breath) associated with chronic renal failure in adult patients, Anaemia is a blood disorder characterised by a decrease in red blood cells. Dynepo may be used in patients on dialysis (a blood clearance technique) or in patients not on dialysis.

2. BEFORE YOU TAKE DYNEPO

Do not take Dynepo:
- if you are allergic (hypersensitive) to epoetin delta or any of the other ingredients of Dynepo.
- if you have difficulties controlling your blood pressure.

Take special care with Dynepo:
Your doctor will closely monitor your haemoglobin concentration level to keep it within the target range of 10 to 12 g/dl and may therefore need to change your dosage of Dynepo accordingly. Occasionally, your individual haemoglobin values may be above and below this recommended target level. Your doctor will manage your dosage so that haemoglobin concentrations will not consistently be above 12 g/dl which may be associated with a higher risk of cardiovascular events (e.g. heart attacks).

Your blood pressure needs to be checked closely before and during treatment with Dynepo. If your blood pressure rises, your doctor may give you medicines to reduce your blood pressure or increase the dosage of your existing blood pressure lowering medication. It may also be necessary to reduce your dose of Dynepo or to stop the treatment for a short period of time.

If you have severe headache, stabbing migraine-like headaches or fits, you should see your doctor at once. It could be a consequence of a marked rise in your blood pressure.

Your doctor will measure your blood iron level during treatment with Dynepo and may give you iron supplements.

Your doctor will monitor the different chemical levels in your blood including: creatinine, potassium.

During dialysis, an increase in the dose of the anticoagulation treatment is frequently required since the increased number of red blood cells may cause blocking of the dialysis tubes.

Dynepo may not be suitable for patients under 18 years old, or for patients with renal or liver problems.

Dynepo should not be used by healthy persons. Severe reactions, possibly fatal, involving the heart and blood vessels may occur.

Dynepo is not approved for use in cancer patients.

Taking other medicines
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.
However, so far, no interactions with other medicines have been reported during treatment with Dynepo.

Taking Dynepo with food and drink
Food and drink has no influence on Dynepo.

Pregnancy and breast-feeding
Inform your doctor if you are pregnant or breast-feeding or think you might be pregnant.
Your doctor will consider what is the best treatment for you during your pregnancy.

Driving and using machines
No effects on ability to drive and use machines have been observed.

3. HOW TO TAKE DYNEPO

Your doctor will be experienced in the treatment of renal failure and the use of erythropoietin. Your first dose will be given under medical supervision as rarely, an allergic-type reaction may occur.

Dynepo may be administered intravenously (into a vein) or subcutaneously (under the skin). In patients not on haemodialysis, where intravenous access is not readily available, Dynepo is usually given subcutaneously.
When given subcutaneously, the site of injection should be changed with each injection.

Your dose of Dynepo will be determined by your doctor and will be adjusted individually according to your personal needs.

Your doctor should maintain your haemoglobin level within the target range of 10 to 12 g/dl. Occasionally, your individual haemoglobin values may be below and above this recommended target level. However your haemoglobin level should not consistently exceed 12 g/dl. You will be monitored

closely to ensure the lowest dose of Dynepo is used to provide adequate control of your symptoms of anaemia.

Always take Dynepo exactly as your doctor has told you to. You should check with your doctor or pharmacist if you are not sure.

The usual starting dose is 50 IU/kg three times a week if administered intravenously or 50 IU/kg twice a week if administered subcutaneously.

The maintenance dose will be then decided by your doctor to maintain the level of your haemoglobin within the target range.

Mainly because of the time required for the production of new red blood cells, an interval of approximately 4 weeks may occur between the dose and an improvement in your anaemia. Your doctor will probably not make changes to your dosage more than once a month.
After any change to the dose, you will have frequent blood tests (once a week) until your haemoglobin level reaches the target range. Your haemoglobin level should then be controlled at regular intervals.

Dynepo therapy is usually a long-term treatment.

If you take more Dynepo than you should
Dynepo can be given in a very large range of doses. If you accidentally give yourself too large a dose, tell your doctor. It may be necessary to monitor your blood.

If you forget to take Dynepo:
Do not take a double dose to make up for a forgotten individual dose. Take your next dose at the normal time.

If you stop taking Dynepo
Do not stop taking Dynepo before discussing the implications with your doctor or pharmacist.

Injecting Dynepo yourself
Your doctor may decide that it would be best for you to inject Dynepo yourself. Your doctor or nurse will show you how to inject yourself. Do not try to inject yourself if you have not been trained.

For information on how to inject Dynepo yourself, please read the instructions at the end of this leaflet.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Dynepo can cause side effects, although not everybody gets them.

If any of the side effects get serious, or if you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

The most frequent side effects observed (in 1% to 10% of patients) with Dynepo are:
- increase in blood pressure. Even patients with normal blood pressure may have a marked rise in their blood pressure and existing high blood pressure can get worse (See 2. Before you take Dynepo).
- if you are on haemodialysis you may experience blockage of the dialysis tubes as your anaemia improves (increase in red blood cells). An increase in the dose of the anticoagulation treatment is frequently required to prevent the blockage occurring.
- headache

Other side effects that occur less frequently (in 0.1% to 1% of patients) include itching, pain, reaction at the site of injection (such as soreness and bleeding), flu-syndrome, diarrhoea, nausea.

Convulsions have been rarely reported (less than 1 every 1000 patients).

Dynepo may also cause changes in the composition of your blood. This includes increase in the number of red blood cells and in the number of platelets.
There may be also changes in the chemistry of your blood, including increase of creatinine, potassium levels.

5. HOW TO STORE DYNEPO

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the carton and on the label of the syringe after "EXP". The expiry date refers to the last day of the month.

Store in a refrigerator (2°C to 8°C). Keep the container in the outer carton in order to protect from light. Do not freeze.

Unopened pre-filled syringes may be kept un-refrigerated but below 25°C for a sinlge maximum period of 5 days. The 5 day period must end before the expiry date stated on the carton and label of the syringe after 'EXP'. Following 5 days storage at below 25°C the pre-filled syringes must be discarded.

The solution is clear, colourless and waterlike with no visible particles. Do not use it if it is cloudy or has visible particles. Do not shake the syringe before use.

Discard the syringe after initial single use.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Dynepo contains

- The active substance is epoetin delta, 0.5 ml of the solution containing 1,000 IU (International Units) (2,000 IU/ml), 0.5 ml of the solution containing 2,000 IU (4,000 IU/ml), 0.3 ml of the solution containing 3,000 IU (10,000 IU/ml), 0.4ml of the solution containing 4,000 IU (10,000 IU/ml), 0.5 ml of the solution containing 5,000 IU (10,000 IU/ml), 0.3 ml of the solution containing 6,000 IU (20,000 IU/ml), 0.4 ml of the solution containing 8,000 IU (20,000 IU/ml), or 0.5 ml of the solution containing 10,000 IU/ml (20,000 IU/ml) of epoetin delta.
- The other ingredients of Dynepo are sodium phosphate monobasic (monohydrate), sodium phosphate dibasic (heptahydrate), polysorbate 20, sodium chloride and water for injections

Dynepo contains less than 1mmol of sodium (23 mg) per dose, i.e. it is essentially "sodium-free".

What Dynepo looks like and contents of the pack

Solution for injection in a pre-filled syringe.

The dosage of solution is:
- 1,000 IU in 0.5 ml
- 2,000 IU in 0.5 ml
- 3,000 IU in 0.3 ml
- 4,000 IU in 0.4 ml
- 5,000 IU in 0.5 ml
- 6,000 IU in 0.3 ml
- 8,000 IU in 0.4 ml
- 10,000 IU in 0.5 ml

Available in packs of 6 pre-filled syringes.

Dynepo is a clear, colourless and waterlike solution for injection containing epoetin delta.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation holder for Dynepo is Shire Pharmaceutical Contracts Ltd, Hampshire International Business Park, Chineham, Basingstoke, Hampshire, RG24 8EP, United Kingdom

The manufacturer is Shire Human Genetic Therapies AB, Åldermansgatan 2, P.O. Box 1117 SE-221 04 Lund, Sweden.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

Belgique/België/Belgien,
Shire Pharmaceuticals Ltd
Hampshire International Business Park,
Chineham, Basingstoke
Hampshire, RG 24 8EP
Vereinigtes Königreich/Royaume-Uni, Verenigd Kononkrijk
Tel. : +44 1256 894 894

Luxembourg/Luxemburg
Shire Pharmaceuticals Ltd
Hampshire International Business Park,
Chineham, Basingstoke
Hampshire, RG 24 8EP,
Vereinigtes Königreich/Royaume-Uni
Tel. : +44 1256 894 894

България / Česká Republika/ Danmark/ Eesti/ Ελλάδα/ Ireland/ Ísland/ Κύπρος/ Latvija/ Lietuva/ Magyarország/ Malta/ Nederland/ Norge/ Österreich/Polska/ România/ Slovenija/ Slovenská Republika/ Suomi/ Sverige/United Kingdom

Shire Pharmaceuticals Ltd
Hampshire International Business Park,
Chineham, Basingstoke
Hampshire, RG 24 8EP,
Великобритания /Velká Británie/Storbritannien/Ühendkuningriik/ Ηνωμένο Βασίλειο/United Kingdom/Bretland/ Lielbritānija/Jungtinė Karalystė/Nagy-Britannia/Verenigd Koninkrijk/ Storbritannia/Wielka Brytania/ Marea Britanie /Velika Britanija/Vel'ká Británia/Iso-Britannia/Storbritannien
Tel/Tlf/Τηλ/Sími/Puh: +44 1256 894 894

France
Shire France S.A.
88, rue du Dome
92514 Boulogne-Billancourt Cedex
Tel.: +33 (1) 46 10 90 00

Deutschland
Shire Deutschland GmbH
Siegburger Str. 229b
50679 Köln
Tel.: + 49 221 802 500

Portugal
Shire Pharmaceuticals Iberica, S.L.
Paseo Pintor Rosales, 40 Bajo Izda.
28008 Madrid, Espanha
Tel. : +34 91 550 06 91

España
Shire Pharmaceuticals Iberica, S.L.
Paseo Pintor Rosales, 40 Bajo Izda.
28008 Madrid
Tel. : +34 91 550 06 91

Italia
Shire Italia S.p.A
Corso Italia, 29
50123 Firenze Tel.: + 39 055 288860

This leaflet was last approved on MM/YYYY

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.

Information on how to give yourself an injection of Dynepo

This section contains information on how to give yourself an injection of Dynepo. It is important that you do not try to give yourself the injection unless you have received special training from your doctor or nurse. Dynepo is provided with a needle guard for your protection and you will be shown how to

use this by your doctor or nurse. If you are not sure about giving the injection or you have any questions, please ask your doctor or nurse for help.

How do I inject Dynepo myself?

You will need to give yourself an injection into the tissue under the skin, known as a subcutaneous injection. Your dose of Dynepo may vary depending on your weight and on your response to the treatment. Your doctor or nurse will tell you how much Dynepo you need and how frequently it should be injected.

Equipment that you need

To give yourself a subcutaneous injection you will need a new pre-filled syringe of Dynepo with needle guard.

What should I do before I give myself a subcutaneous injection of Dynepo?

1. Take your Dynepo pre-filled syringe out of the refrigerator.
2. Do not shake the pre-filled syringe.
3. Check that it is the correct dose that your doctor has prescribed.
4. Check the expiry date on the pre-filled syringe label (EXP:). Do not use it if the date has passed the last day of the month shown.
5. Check the appearance of Dynepo. It must be clear. If it is cloudy or there are particles in it, you must not use it.
6. For a more comfortable injection, let the pre-filled syringe stand for 30 minutes to reach room temperature or hold the pre-filled syringe gently in you hand for a few minutes. **Do not** warm Dynepo in any other way (for example, do not warm it in a microwave or in hot water).
7. **Do not** remove the cover from the syringe until you are ready to inject.
8. **Wash your hands thoroughly.**

Find a comfortable, well-lit place and put the Dynepo pre-filled syringe where you can reach it.

How do I prepare my Dynepo injection?

Before you inject Dynepo you must do the following:

1. Hold the syringe assembly by the sides of the device and gently remove the plastic cover and rubber guard from the needle without twisting. Pull straight. Do not touch the needle or push the plunger.
2. You may notice a small air bubble in the pre-filled syringe. You do not have to remove the air bubble before injecting. Injecting the solution with the air bubble is harmless.
3. You can now use the pre-filled syringe.

Where should I give my injection?

The most suitable places to inject yourself are:

- The top of your thighs; and
- The abdomen, except for the area around the naval.

Change the place that you inject each time so you don't become sore in one area. If someone else is injecting for you, they can also use the back of your arms.

How do I give my injection?

1. Clean your skin and then pinch the skin between your thumb and forefinger, without squeezing it.
2. Put the needle fully into the skin as shown by your nurse or doctor.
3. Pull slightly on the plunger to check that a blood vessel has not been punctured. If you see blood in the syringe, remove the needle and put it in another place.
4. Depress the plunger slowly and evenly while holding the syringe barrel, always keeping your skin pinched.
5. Ensure that you only inject the amount as instructed by your doctor or nurse.
6. After injecting the liquid, remove the needle and let go of your skin.
7. Let go of the plunger allowing the syringe to move up inside the device until the entire needle is guarded.
8. Only use each syringe for one injection.

Remember

If you have any problems, please do not be afraid to ask your doctor or nurse for help and advice.

Disposing of used syringes

Your Dynepo syringe is provided with a needle guard to prevent needle stick injuries after use, so no special disposal precautions are required.