

AUSTRALIAN PRODUCT INFORMATION
Mircera® (methoxy polyethylene glycol-epoetin beta)

1. NAME OF THE MEDICINE

Methoxy polyethylene glycol-epoetin beta

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mircera 30 micrograms/0.3 mL solution for injection in pre-filled syringe

Mircera 50 micrograms/0.3 mL solution for injection in pre-filled syringe

Mircera 75 micrograms/0.3 mL solution for injection in pre-filled syringe

Mircera 100 micrograms/0.3 mL solution for injection in pre-filled syringe

Mircera 120 micrograms/0.3 mL solution for injection in pre-filled syringe

Mircera 150 micrograms/0.3 mL solution for injection in pre-filled syringe

Mircera 200 micrograms/0.3 mL solution for injection in pre-filled syringe

Mircera 250 micrograms/0.3 mL solution for injection in pre-filled syringe

Mircera 360 micrograms/0.6 mL solution for injection in pre-filled syringe

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

The solution is clear and colourless to slightly yellowish and the pH is 6.2

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Mircera is indicated for the treatment of anaemia associated with chronic kidney disease (CKD).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

General

Use the lowest dose of Mircera that will gradually increase the haemoglobin concentration. Mircera is administered less frequently than Aranesp®, Eprex® and NeoRecormon® due to the longer elimination half-life.

Treatment with Mircera is to be initiated under the supervision of a healthcare professional.

Treatment of Anaemic Patients with Chronic Kidney Disease

The solution can be administered by subcutaneous (SC) or intravenous (IV) injection, according to clinical preference. Mircera can be injected SC in the abdomen, arm or thigh. All three injection sites are equally suitable for SC injection with Mircera.

Patients being changed from SC to IV administration of Mircera (or vice-versa) should have their haemoglobin levels monitored to ensure that the haemoglobin concentration stays within the desired target of 100 and 120 g/L. Patients should be monitored closely to ensure that the lowest effective dose of Mircera is used to provide adequate control of the symptoms of anaemia.

Patients not currently treated with an Erythropoiesis Stimulating Agent (ESA): *Patients not on dialysis* - The recommended starting dose is 1.2 µg/kg body weight administered once every month as a single SC injection. Alternatively, a starting dose of 0.6 µg/kg body weight may be administered once every two weeks as a single IV or SC injection.

Patients on dialysis – The recommended starting dose of 0.6 µg/kg body weight may be administered once every two weeks as a single IV or SC injection.

It is recommended that haemoglobin is monitored every two weeks until stabilised, and periodically thereafter (see section 4.4 Special warnings and precautions for use).

The dose of Mircerca may be increased by approximately 25% of the previous dose if the rate of rise in haemoglobin is less than 10 g/L over a month. Further increases of approximately 25% may be made at monthly intervals until the individual target haemoglobin level is obtained.

Dose adjustments should not be made more frequently than once a month. The dose for each patient should be adjusted so that the haemoglobin level does not exceed 120 g/L. If the rate of rise in haemoglobin is greater than 20g/L in one month or the haemoglobin level is increasing and approaching 120 g/L, the Mircerca dose should be reduced by approximately 25%.

If the haemoglobin level continues to increase following dose reduction, the dose should be temporarily withheld until the haemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the haemoglobin increases by more than 10 g/L in any 2 week period, the dose should be decreased by approximately 25%. After dose interruption, a haemoglobin decrease of approximately 3.5 g/L per week is expected.

Patients treated once every two weeks whose target haemoglobin has been reached may receive Mircerca administered once monthly using the dose equal to twice the previous fortnightly dose.

Patients currently treated with an Erythropoiesis Stimulating Agent (ESA):

When converting from epoetin or darbepoetin alfa, Mircerca can be administered once monthly or, if desired, once every two weeks as a single IV or SC injection. The starting dose of Mircerca is calculated based on the previously-given ESA weekly dose at the time of conversion, as described in Table 1 below. The two-weekly dose should be approximately half the once monthly dose. The first injection of Mircerca should be administered at the next scheduled dose of the previously administered darbepoetin alfa or epoetin.

Table 1. Mircerca dose when converting from another ESA

Previous Weekly Darbepoetin Alfa Dose (µg/week)	Previous Weekly Epoetin Dose (Units/week)	Mircera Starting Dose (µg/month)
< 40	< 8000	120
40-80	8000-16000	200
> 80	> 16000	360

It is recommended that haemoglobin is monitored every month until stabilised, and periodically thereafter (see section 4.4 Special warnings and precautions for use).

If a dose adjustment is required to maintain the target haemoglobin concentration between 100 - 120 g/L, the monthly dose may be adjusted by approximately 25%.

Dose adjustments should not be made more frequently than once a month. The dose for each patient should be adjusted so that the haemoglobin level does not exceed 120 g/L. If the haemoglobin is increasing and approaching 120 g/L, the dose should be reduced by approximately 25%. If the

haemoglobin continues to increase following dose reduction, the dose should be temporarily withheld until the haemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the haemoglobin increases by more than 10 g/L in any 2 week period, the dose should be decreased by approximately 25%. After dose interruption, a haemoglobin decrease of approximately 3.5 g/L per week is expected.

Treatment Interruption

Treatment with Mircera is normally long-term. However, it can be interrupted at any time, if necessary.

Missed Dose

If one dose of Mircera is missed, the missed dose should be administered as soon as possible and administration of Mircera restarted at the prescribed dosing frequency.

Dosage adjustment

Hepatic Impairment

No adjustments of the starting dose or dose modification rules are required in patients with any degree of hepatic impairment.

4.3 CONTRAINDICATIONS

Mircera is contraindicated in patients with:

- Uncontrolled hypertension.
- Known hypersensitivity to the active substance or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Serious allergic reactions including pruritis and rash, have been reported in patients treated with Mircera. If a serious allergic or anaphylactic reaction occurs due to Mircera, treatment should be immediately discontinued and appropriate therapy should be administered.

Cardiovascular and Thrombotic Events / Increased Mortality

Cardiovascular and thrombotic events such as myocardial ischaemia and infarction, cerebrovascular haemorrhage and infarction, transient ischaemic attacks, deep venous thrombosis, arterial thrombosis, pulmonary emboli, retinal thrombosis and haemodialysis graft occlusion have been reported in patients receiving ESAs.

In controlled clinical trials, ESAs increased the risk for death in oncology patients and for serious cardiovascular events in oncology and CKD patients when administered to target a haemoglobin of > 120 g/L. There was an increased risk of serious arterial and venous thromboembolic events, including myocardial infarction, stroke, congestive heart failure and haemodialysis graft occlusion. A rate of haemoglobin rise of > 10 g/L over 2 weeks may also contribute to these risks.

ESAs also increased the risk of thrombosis in patients undergoing orthopaedic procedures or coronary artery bypass.

The safety and efficacy of Mircera have not been established in patients with anaemia due to cancer chemotherapy or in the peri-surgical setting.

To reduce cardiovascular risks, use the lowest dose of Mircera that will gradually increase the haemoglobin concentration. The haemoglobin concentration should not exceed 120 g/L and the rate of haemoglobin increase should not exceed 10 g/L in a 2 week period. Haemoglobin levels should

be checked at regular intervals and dosages adjusted (see section 4.2 Dose and method of administration).

Growth Factor Potential / Increased Tumour Progression

Mircera, like other ESAs, is a growth factor that primarily stimulates red blood cell (RBC) production. As with all growth factors, there is a theoretical concern that epoetins could act as a growth factor for any type of malignancy. ESAs, when administered to target haemoglobin of > 120 g/L, shortened the time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy. ESAs also shortened the time to tumour progression and/or survival in patients with breast cancer, cervical cancer, lymphoid malignancy or non-small cell lung cancer when administered to a target haemoglobin \geq 120 g/L. Although the target haemoglobin was \geq 120 g/L, the risk of accelerated tumour progression and shortened survival has not been excluded when ESAs are used to target haemoglobin < 120 g/L.

ESAs have been associated with an increased risk of thrombosis (see section 4.4 Special warnings and precautions for use) and accelerated tumour progression. Mircera is not indicated for the treatment of anaemia in patients with cancer.

Hypertension

Patients with uncontrolled hypertension should not be treated with Mircera; blood pressure should be adequately controlled before initiation of therapy. Blood pressure may rise during treatment of anaemia with Mircera as with other ESAs. Hypertensive encephalopathy and seizures have been observed in patients treated with Mircera as with other ESAs.

Special care should be taken to closely monitor and control blood pressure in patients treated with Mircera. During Mircera therapy, patients should be advised of the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control after initiation of appropriate measures, the dose of Mircera should be reduced or temporarily withheld until haemoglobin begins to decrease (see section 4.2 Dose and method of administration).

Pure Red Cell Aplasia (PRCA)

PRCA caused by neutralising anti-erythropoietin antibodies has been reported in association with ESA therapy including Mircera. These antibodies have been shown to cross-react with all erythropoietic proteins, and patients suspected or confirmed to have neutralising antibodies to erythropoietin should not be switched to Mircera. If anti-erythropoietin antibody-mediated PRCA develops whilst on Mircera, therapy with Mircera must be discontinued and patients should not be switched to another ESA.

Seizures

ESAs should be used with caution in patients with epilepsy.

Severe cutaneous adverse reactions

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

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Mircera should be withdrawn immediately and an alternative treatment considered.

If the patient has developed a severe cutaneous skin reaction such as SJS or TEN due to the use of Mircera, treatment with Mircera must not be restarted in this patient at any time.

General

The safety and efficacy of Mircera therapy have not been established in patients with haemoglobinopathies or with a platelet level greater than $500 \times 10^9/L$. Therefore, caution should be used in these patients.

Supplementary iron therapy is recommended for all patients with serum ferritin values below $100 \mu\text{g/L}$ or whose transferrin saturation is below 20%, as per Caring for Australasians with Renal Impairment (CARI) Guidelines. To ensure effective erythropoiesis, iron status should be evaluated for all patients prior to, and during treatment.

A lack of response or failure to maintain haemoglobin response with Mircera within the recommended dose range should prompt a search for causative factors. Deficiencies of iron, folic acid, and vitamin B₁₂ should be excluded or corrected. The following conditions may also compromise the effectiveness of ESA therapy: chronic blood loss, bone marrow fibrosis, haemolysis, and severe aluminium overload due to treatment of renal failure. If all these conditions are excluded and the patient has a sudden drop of haemoglobin associated with reticulocytopenia and anti-erythropoietin antibodies, examination of the bone marrow for the diagnosis of PRCA should be considered. If PRCA is diagnosed, therapy with Mircera must be discontinued and patients should not be switched to another ESA.

Misuse by non-anaemic persons may lead to an excessive increase in haemoglobin. This may be associated with life threatening complications of the cardiovascular system.

Paediatric Use

Mircera is not recommended for use in patients aged less than 18 years due to a lack of data on safety and efficacy.

Use in the Elderly

Of the 1789 CKD patients treated with Mircera in clinical trials, 24% were aged 65 to 74 years, while 20% were aged 75 years and over. Based on population analyses, no adjustment of the starting dose is required in patients aged 65 years or older.

Effects on Laboratory Tests

Refer to section 4.8 Adverse Effects (Undesirable Effects).

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No interaction studies have been performed. The results from clinical trials do not indicate any interaction of Mircera with other medicinal products. There was no indication of an effect of concomitant medications on the pharmacokinetics and pharmacodynamics of Mircera using a population analysis approach.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

When Mircera was administered subcutaneously to male and female rats prior to, and during mating, at 6 times the clinical systemic exposure, based on AUC values, fertility, and sperm count and motility were not affected.

Use in Pregnancy - Category B3

Methoxy polyethylene glycol-epoetin beta crossed the rat placenta and was distributed to foetal tissues, particularly the reproductive organs, spleen and kidneys. A reduction in foetal weights occurred in rats and rabbits at systemic exposures 1 to 3 times clinical exposure, with an increase in reversible developmental delays, such as incomplete ossification, in both species. In rabbits there was an increase in the incidence of flat ribs at 29 times the clinical systemic exposure (based on AUC values). All doses tested in both species caused exaggerated pharmacodynamic effects in dams. Post-implantation loss was increased in rabbits and sometimes in rats. Mircera should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

It is unknown whether Mircera is excreted in human breast milk. Methoxy polyethylene glycol-epoetin beta was excreted into the milk of rats. Mircera treatment of lactating rats was associated with some adverse effects on the offspring, which included reduced pup bodyweight gain, developmental delay, slightly increased pup mortality, increased incidence of pale livers and/or lungs and an increase in the incidence of abdominal distension post weaning. A decision on whether to discontinue breast-feeding or therapy with Mircera should be made taking into account the benefit of Mircera therapy to the woman and the potential risks to the child.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However, no effects are expected based on the mechanism of action and the known safety profile of Mircera.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials

The safety database for Mircera (based on data from the completed phase II and III studies and long-term follow-up information from safety extension studies) comprised of 2737 CKD patients, where 1789 were treated with Mircera and 948 with another ESA.

Based on the results of 1789 patients, approximately 8% of patients treated with Mircera experienced adverse reactions. The most frequently reported adverse reaction was hypertension.

Adverse events (irrespective of causal relationship) with $\geq 5\%$ incidence in patients treated with Mircera or a reference drug (epoetin or darbepoetin alfa) are presented in Table 2.

Table 2. Adverse events (irrespective of causal relationship) occurring in $\geq 5\%$ of CKD patients

Adverse Event	Mircera (n = 1789)	Epoetin or Darbepoetin alfa (n = 948)
Vascular		
Hypertension	19%	21%
Hypotension	7%	7%
Gastrointestinal		
Diarrhoea	17%	19%
Vomiting	9%	11%
Constipation	7%	9%
Nausea	7%	8%
Abdominal Pain	5%	5%
Dyspepsia	4%	5%
Infections and infestations		
Nasopharyngitis	15%	15%
Upper Respiratory Tract Infection	11%	12%
Urinary Tract Infection	9%	10%
Bronchitis	7%	8%
Pneumonia	7%	9%
Influenza	6%	6%
Gastroenteritis	5%	6%

Adverse Event	Mircera (n = 1789)	Epoetin or Darbepoetin alfa (n = 948)
Nervous system		
Headache	13%	13%
Dizziness	6%	6%
Injury, poisoning and procedural complications		
Procedural Hypotension	13%	11%
Arteriovenous Fistula Thrombosis	8%	8%
Arteriovenous Fistula Site Complication	8%	9%
Arteriovenous Graft Thrombosis	6%	7%
Arteriovenous Fistula Site Haemorrhage	5%	5%
Contusion	4%	5%
Musculoskeletal and connective tissue		
Muscle Spasms	11%	12%
Back Pain	10%	9%
Pain in Extremity	8%	9%
Arthralgia	7%	8%
Respiratory, thoracic and mediastinal		
Cough	10%	10%
Dyspnoea	6%	8%
Metabolism and nutrition		
Fluid Overload	10%	9%
Hyperkalaemia	5%	6%
Hypoglycaemia	3%	6%
General and administration site complications		
Pyrexia	7%	7%
Oedema Peripheral	4%	7%
Asthenia	5%	4%
Skin and subcutaneous tissue disorders		
Pruritus	6%	7%
Psychiatric disorders		
Insomnia	6%	6%
Cardiac disorders		
Angina Pectoris	6%	5%
Cardiac Failure Congestive	4%	5%
Renal and urinary disorders		
Renal Failure Chronic	5%	7%
Blood and lymphatic system disorders		
Anaemia	5%	4%

The adverse event of thrombocytopenia was reported in 0.8% of Mircera treated patients and 0.5% of patients receiving epoetin or darbepoetin alfa, irrespective of causal relationship. However, the

incidence of platelet count less than $100 \times 10^9/L$ was considerably higher in both treatment groups (see section 4.4 Special warnings and precautions for use).

Platelet count and thrombocytopenia

During treatment with Mircera, a slight decrease (median 5.7%) in platelet counts, remaining within the normal range, was observed in clinical studies. The decline was observed after the first dose and there was a partial recovery over the course of the studies.

A platelet count below $100 \times 10^9/L$ was observed in 9.0% of patients treated with Mircera and 6.2% of patients treated with other ESAs.

Some of the adverse events reported are typically associated with CKD, or recognised complications of dialysis, and may not necessarily be attributable to Mircera therapy.

The following descriptors are used to describe the frequency of adverse reactions attributed to treatment with Mircera in controlled clinical trials:

Common ($\geq 1/100$ and $< 1/10$), Uncommon ($\geq 1/1000$ and $< 1/100$), and Rare ($\geq 1/10,000$ and $< 1/1000$).

Vascular disorders: *common* hypertension; *rare* hot flush

Injury, poisoning and procedural complications: *uncommon* vascular access thrombosis

Immune system disorders: *rare* hypersensitivity, anaphylactic reaction (not known)

Nervous system disorders: *uncommon* headache; *rare* hypertensive encephalopathy

Skin and subcutaneous tissue disorders: *rare* rash (maculo-papular, serious)

All other events attributed to Mircera were reported with rare frequency and were of mild to moderate severity in the majority of patients. These events were consistent with co-morbidities known in the population.

Post-Marketing Experience

Neutralising anti-erythropoietin antibody-mediated pure red cell aplasia (AEAB-PRCA) associated with Mircera therapy has been reported during post marketing experience (see section 4.4 Special warnings and precautions for use). Stevens-Johnson syndrome / toxic epidermal necrolysis has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems

4.9 OVERDOSE

The therapeutic range of Mircera is wide and individual response to therapy must be considered when Mircera treatment is initiated. Overdose can result in manifestations of an exaggerated pharmacodynamic effect, e.g. excessive erythropoiesis. In case of excessive haemoglobin levels, Mircera should be temporarily withheld. If clinically indicated, phlebotomy may be performed.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other antianemic preparations, ATC code: B03XA03.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Mircera shows different activity to recombinant erythropoietin at the receptor level. It is characterised by slower association to the receptor and slightly faster dissociation, resulting in a lower affinity for the receptor. This lower affinity may result in less receptor-mediated endocytosis and contribute together with reduced subsequent lysosomal degradation and/or increased recycling to the slower elimination. Mircera thus has a longer half-life than erythropoietin which enables Mircera to be administered in a once monthly dosing regimen.

Erythropoietin is a growth factor for erythroid development. It is produced in the kidney and released into the bloodstream in response to hypoxia, interacting with erythroid progenitor cells to increase red blood cell production. Production of endogenous erythropoietin is impaired in patients with chronic kidney disease (CKD), and erythropoietin deficiency is the primary cause of their anaemia.

The onset of haemoglobin increase (defined as an increase > 4 g/L from baseline) is observed in CKD patients after 7 to 15 days following a single dose of Mircera.

Clinical trials

Chronic Kidney Disease Anaemia

Mircera has been evaluated in patients not currently treated with an ESA (including patients on dialysis and not on dialysis) and those currently treated with an ESA.

Patients Not Currently Treated with an Erythropoiesis Stimulating Agent (ESA)

Table 3. Summary of phase III trials in anaemic CKD patients not currently treated with an ESA

	CORDATUS (n = 307)	ARCTOS (n = 324)	AMICUS (n = 181)
Study design / Patient group	Open-label, randomised, CKD patients not on dialysis No prior ESA treatment	Open-label, randomised CKD patients not on dialysis No prior ESA treatment	Open-label, randomised CKD patients on dialysis No prior ESA treatment
Patient numbers	Mircera (n = 153) Darbepoetin alfa (n = 154)	Mircera (n = 162) Darbepoetin alfa (n = 162)	Mircera (n = 135) Epo alfa or epo beta (n = 46)
Duration of treatment	28 wk 20 wk initiation, 8 wk maintenance	52 wk 28 wk initiation, 24 wk maintenance	52 wk 24 wk initiation, 28 wk maintenance
Route / Starting dose / Dosage regimen	<u>Mircera:</u> SC: 1.2 µg/kg, q4w <u>Darbepoetin alfa:</u> SC: 0.45 µg/kg, q1w or 0.75 µg/kg, q2w Target Hb: 100 to 120 g/L	<u>Mircera:</u> SC: 0.6 µg/kg Initiation: q2w Maintenance: q2w or q4w <u>Darbepoetin alfa:</u> SC: 0.45 µg/kg Initiation: q1w Maintenance: q1w or q2w Target Hb: 110 to 130 g/L.	<u>Mircera:</u> IV: 0.4 µg/kg Initiation: q2w Maintenance: q2w or q4w <u>Epo alfa or epo beta</u> IV: dose per label Initiation & maintenance: 3x/wk Target Hb: 110 to 130 g/L.
Efficacy results	<u>Hb response[#]</u> Mircera: 94.1% (95% CI: 89.1, 97.3) Darbepoetin alfa: 93.5% (95% CI: 88.4, 96.8)	<u>Hb response[*]</u> Mircera: 97.5% (95% CI: 93.8, 99.3) Darbepoetin alfa: 96.3% (95% CI: 92.1, 98.6)	<u>Hb response[*]</u> Mircera: 93% (95% CI: 87.7, 96.9) Epo alfa or epo beta: 91% (95% CI: 79.2, 97.6)
	<u>Median time to Hb response</u> Mircera: 43 days Darbepoetin alfa: 29 days	<u>Median time to Hb response</u> Mircera: 43 days Darbepoetin alfa: 29 days	<u>Median time to Hb response</u> Mircera: 57 days Epo alfa or epo beta: 31 days
	<u>Hb change from baseline</u> Mircera: 16.2 g/L Darbepoetin alfa: 16.6 g/L (p < 0.0001)	<u>Hb change from baseline</u> Mircera: 21.5 g/L Darbepoetin alfa: 19.9 g/L (p < 0.0001)	
	<u>Incidence of RBC transfusion</u> Mircera: 3.3% Darbepoetin alfa: 6.5%	<u>Incidence of RBC transfusion</u> Mircera: 2.5% Darbepoetin alfa: 6.8%	<u>Incidence of RBC transfusion</u> Mircera: 5.2% Epo alfa or beta: 4.3%

[#] Hb response defined as at least a 10 g/L increase in Hb concentration to a level of at least 100 g/L without RBC transfusion.

^{*} Hb response defined as at least a 10 g/L increase in Hb concentration to a level of at least 110 g/L without RBC transfusion.

CKD = Chronic Kidney Disease, ESA = Erythropoiesis Stimulating Agent, q1w = once weekly, q2w = once every two weeks, q4w = once every four weeks, Hb = haemoglobin, RBC = red blood cell, Epo = epoetin, IV = intravenous, SC = subcutaneous, wk = week, CI = confidence interval.

The change in haemoglobin levels (from baseline) observed in these clinical trials demonstrated Mircera to be clinically non-inferior to darbepoetin alfa (p < 0.0001). The time to haemoglobin response was longer with Mircera than the comparator. For the ARCTOS and AMICUS trials the observed median dose of Mircera (once every two weeks) was 0.6 µg/kg.

A lower proportion of patients treated with Mircera experienced a haemoglobin level greater than 130 g/L during the first 8 weeks of treatment compared to the reference arms in the AMICUS and ARCTOS studies (7.5% in the Mircera group compared to 17.8% for epoetin alfa or beta and 34% in the darbepoetin alfa arm compared to 11.4% for Mircera). The corresponding proportions of patients experiencing a haemoglobin level greater than 120 g/L during the first 8 weeks of treatment in the CORDATUS study were 25.8% in the Mircera group and 47.7% in the darbepoetin alfa group.

Patients Currently Treated with an Erythropoiesis Stimulating Agent (ESA)

CKD patients currently receiving an ESA were randomised to stay on their current treatment or switched to Mircera to maintain stable haemoglobin levels. For patients randomised to receive Mircera (either once every two weeks or once every four weeks) the initial dose was determined based on the patient's previous weekly ESA dose.

Table 4. Summary of phase III trials in anaemic CKD patients currently receiving an ESA

	MAXIMA (n = 673)	PROTOS (n = 572)	STRIATA (n = 313)	RUBRA (n = 336)
Study design / Patient group	Open-label, randomised CKD dialysis patients with stable Hb* receiving epo (IV)	Open-label, randomised CKD dialysis patients with stable Hb* receiving epo (SC)	Open-label, randomised CKD dialysis patients with stable Hb* on darbepoetin (IV)	Open-label, randomised CKD dialysis patients with stable Hb* receiving epo (SC or IV)
Patient numbers	Mircera (n = 447) Epo alfa or epo beta (n = 226)	Mircera (n = 381) Epo alfa or epo beta (n = 191)	Mircera (n = 157) Darbepoetin alfa (n = 156)	Mircera (n = 168) Epo alfa or epo beta (n = 168)
Duration of treatment	52 wk	52 wk	52 wk	36 wk
Route / Dosage regimen	<u>Mircera:</u> IV: 30, 50, or 90 µg/wk. q2w, q4w <u>Epo alfa or epo beta</u> IV at previous dose and schedule	<u>Mircera:</u> SC: 30, 50, or 90 µg/wk. q2w, q4w <u>Epo alfa or epo beta</u> SC at previous dose and schedule	<u>Mircera:</u> IV: 60, 100, or 180 µg/ q2w <u>Darbepoetin alfa</u> IV at previous dose and schedule	<u>Mircera:</u> IV or SC: 60, 100, or 180 µg/q2w <u>Epo alfa or epo beta</u> IV or SC: at previous dose and schedule
Efficacy results	No difference in Hb change from baseline (p < 0.0001)	No difference in Hb change from baseline (p < 0.0001)	No difference in Hb change from baseline (p < 0.0001)	No difference in Hb change from baseline (p < 0.0001)

* stable Hb baseline Hb concentration between 105 and 130 g/L

CKD = Chronic Kidney Disease, ESA = Erythropoiesis Stimulating Agent, q2w = once every two weeks, q4w = once every 4 weeks, Hb = haemoglobin, Epo = epoetin, IV = intravenous, SC = subcutaneous, wk = week.

The results from these studies demonstrated the ability of Mircera to maintain haemoglobin concentrations within the study target range of 110 - 130 g/L.

The most frequently reported adverse effect in clinical trials (both comparators and Mircera) was hypertension (see section 4.4 Special warnings and precautions for use).

Other Clinical Trials

In a randomised, placebo-controlled, single-blind, three-way crossover study, pain scores after SC injection with Mircera were similar to placebo and significantly less compared to other ESAs.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of Mircera was studied in healthy volunteers and in anaemic CKD patients, including patients on dialysis and not on dialysis.

A comparison of serum concentrations of Mircera measured before and after haemodialysis in 41 CKD patients showed that haemodialysis had no effect on Mircera serum concentrations *in vivo*.

The results of a study in 42 healthy volunteers indicated that the site of subcutaneous (SC) injection (abdomen, arm or thigh) had no clinically relevant effect on the pharmacokinetics, pharmacodynamics, or local tolerability of Mircera. Based on these results, all three sites are considered suitable for SC injection with Mircera.

An analysis in 126 CKD patients showed no pharmacokinetic difference between patients on dialysis and patients not on dialysis.

Multiple dosing in CKD patients was found to have no effect on the clearance, volume of distribution and bioavailability of Mircera

Absorption

Following SC administration in CKD patients, the maximum serum concentrations of Mircera were observed 72 hours (median value) after administration in dialysis patients and 95 hours after administration in patients not on dialysis. The absolute bioavailability of Mircera after SC administration was 62% and 54%, in dialysis patients and patients not on dialysis, respectively

A study in 400 CKD patients showed that the volume of distribution of Mircera is approximately 5 L.

After administration every 4 weeks in CKD patients, there was virtually no accumulation of Mircera, as demonstrated by a ratio of accumulation of 1.03. After administration every 2 weeks, the ratio of accumulation in serum was 1.12.

Excretion

The pharmacokinetic and the pharmacological properties of Mircera allow for monthly administration due to the longer elimination half-life. The elimination half-life after intravenous (IV) administration of Mircera is 15 to 20 times longer compared to recombinant human erythropoietin.

Following IV administration in CKD patients, the observed terminal elimination half-life ($t_{1/2}$) for Mircera was 134 hours, and the total systemic clearance was 0.494 mL/hr/kg. Following SC administration the $t_{1/2}$ was 139 hours in dialysis patients and 142 hours in patients not on dialysis.

Data on methoxy polyethylene glycol-epoetin beta metabolism in animals is not available. In rat, both unchanged methoxy polyethylene glycol-epoetin beta (about 1% of administered dose) and polyethylene glycol-like material were found in urine. In humans, it is unknown whether a significant proportion of methoxy polyethylene glycol-epoetin beta is catabolised. In clinical trials with healthy volunteers, unchanged methoxy polyethylene glycol-epoetin beta was not detected in the urine. Due to its high molecular weight, renal excretion of methoxy polyethylene glycol-epoetin beta would not be expected.

Pharmacokinetics in Special Populations

Population analyses evaluated the potential effects of demographic characteristics on the pharmacokinetics of Mircera. Results of these analyses showed that no dose adjustments are necessary for age, gender, or race.

From a single dose study, it was shown that following IV administration, the pharmacokinetics of Mircera are similar in patients with severe hepatic impairment compared to healthy subjects.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The genotoxic potential of Mircera has not been evaluated.

Carcinogenicity

The carcinogenic potential of Mircera has not been evaluated in long-term animal studies. As with all growth factors, there is a concern that ESAs could stimulate the growth of any type of malignancy (see section 4.4 Special warnings and precautions for use).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Monobasic sodium phosphate monohydrate
Sodium sulfate
Mannitol
Methionine
Poloxamer
Water for injections

6.2 INCOMPATIBILITIES

Mircera should not be mixed with other products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Mircera must not be used after the expiry date.

Store continuously in the refrigerator at 2°C to 8°C. Do not freeze. Do not shake. Protect from light.

The prefilled syringes contain no antimicrobial preservative and are for single-use in one patient only. Discard any residue.

The end user may remove Mircera from refrigeration (2°C to 8°C) for storage at room temperature (up to 30°C) for one single period of 1 month. Once removed from the fridge, the product must be used within 1 month and not returned to the fridge for storage.

Allow the product to reach room temperature before injecting.

6.5 NATURE AND CONTENTS OF CONTAINER

Mircera is supplied in a pack containing one single-use prefilled syringe and a 27 gauge, ½ inch needle. Each prefilled syringe is equipped with a needle guard that covers the needle during disposal to reduce the risk of needle stick injury after application.

Mircera is available in the following strengths and plungers are colour coded for easy identification as indicated below:

Strength (µg)	Volume (mL)	Colour
30	0.3	aqua
50	0.3	yellow
75	0.3	red
100	0.3	turquoise
120	0.3	lime
150*	0.3	grey
200	0.3	purple
250*	0.3	green
360	0.6	salmon

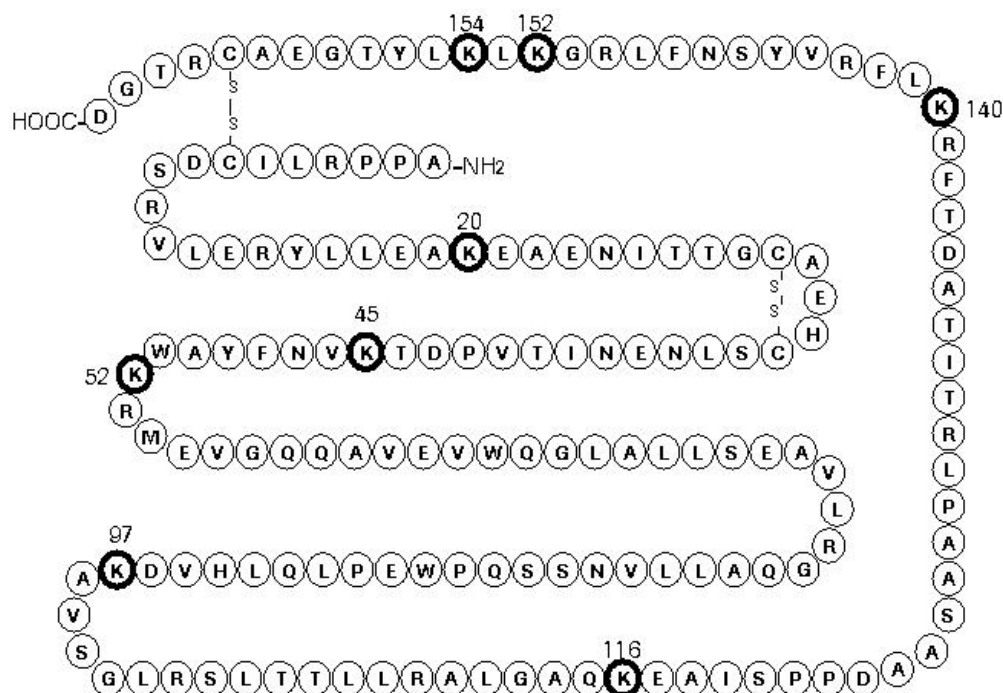
* not currently distributed in Australia

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure



Mircera (methoxy polyethylene glycol-epoetin beta) is a chemically synthesised Erythropoiesis Stimulating Agent (ESA) with a much longer half-life than erythropoietin.

It is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells and differs from erythropoietin through the integration of an amide bond between either the N-terminal amino group or the ε-amino group of lysine, predominantly Lys⁵² and Lys⁴⁵ and methoxy polyethylene glycol butanoic acid. This results in a molecular weight of approximately 60 kDa with the

polyethylene glycol-moiety having an approximate molecular weight of 30 kDa. The dosage strength in µg indicates the quantity of the protein moiety of the methoxy polyethylene glycol-epoetin beta molecule without consideration of glycosylation.

CAS number

677324-53-7

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4. Prescription only medicine.

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 - 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

9 May 2011

10. DATE OF REVISION OF THE TEXT

03 November 2023

Summary table of changes

Section Changed	Summary of new information
4.2	Update to upper dosing recommendation limit for dose increase and reduction