Maklumat tambahan indikasi untuk upload pada laman web
Year 2016
Products Approved For Additional Indication (DCA 307 – 22 Disember 2016)

<table>
<tr><th>NO</th><th>PRODUCT
(ACTIVE INGREDIENT)</th><th>ADDITIONAL INDICATION</th><th>MARKETING AUTHORIZATION HOLDER</th></tr>
<tr>
<td>1.</td>
<td>1.1 Revlimid (Lenalidomide) Capsules 5mg
[Lenalidomide 5mg]

1.2 Revlimid (Lenalidomide) Capsules 10mg
[Lenalidomide 10mg]

1.3 Revlimid (Lenalidomide) Capsules 15mg
[Lenalidomide 15mg]

1.4 Revlimid (Lenalidomide) Capsules 25mg
[Lenalidomide 25mg]

1.5 Revlimid (Lenalidomide) Capsules 5mg
[Lenalidomide 5mg]

1.6 Revlimid (Lenalidomide) Capsules 10mg
[Lenalidomide 10mg]

1.7 Revlimid (Lenalidomide) Capsules 15mg
[Lenalidomide 15mg]

1.8 Revlimid (Lenalidomide) Capsules 25mg
[Lenalidomide 25mg]</td>
<td>➢ Indication:

Revlimid® in combination with dexamethasone is indicated for the treatment of previously untreated multiple myeloma patients who are not eligible for transplant.

➢ Posology:

Newly diagnosed multiple myeloma

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.

<u>Recommended dose</u>
The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). For patients ≥75 years of age, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. The recommended dose of lenalidomide for patients suffering from moderate renal impairment (30 ≤ CLcr < 50 ml/min) is 10 mg once daily.

<u>Recommended dose adjustments during treatment and restart of treatment:</u>
Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

• Dose reduction steps

<table>
<tr><th></th><th>Lenalidomide</th><th>Dexamethasone</th></tr>
<tr><td>Starting dose</td><td>25 mg</td><td>40 mg</td></tr>
<tr><td>Dose level-1</td><td>20 mg</td><td>20 mg</td></tr>
</table>
</td>
<td>CELGENE SDN. BHD.
Lot 6.05, Level 6, KPMG Tower 8
First Avenue, Bandar Utama
47800 Petaling Jaya, Selangor</td>
</tr>
</table>

Dose level-2	*15 mg*	*12 mg*
Dose level-3	*10 mg*	*8 mg*
Dose level-4	*5 mg*	*4 mg*
Dose level-5	*5 mg every other day*	*NA*

- *Thrombocytopenia*

When platelets	*Recommended course*
Fall to < 25 x 10^9/L	*Stop lenalidomide dosing for remainder of cycle[a]*
Return to ≥ 50 x 10^9/L	*Decrease by one dose level when dosing resumed at next cycle*

[a]If Dose Limiting Toxicity (DLT) occurs on > Day 15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

- *Neutropenia*

When neutrophils	*Recommended course*
First fall to < 0.5 x 10^9/L *Return to ≥ 1 x 10^9/L when neutropenia is the only observed toxicity*	*Interrupt lenalidomide treatment* *Resume lenalidomide at Starting dose once daily*
Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	*Resume lenalidomide at Dose level-1 once daily*
For each subsequent drop below < 0.5 x 10^9/L *Return to ≥ 0.5 x10^9/L*	*Interrupt lenalidomide treatment* *Resume lenalidomide at next lower dose level once daily.*

In case of neutropenia, the use of growth factors in patient management should be considered. If the dose of lenalidomide was reduced for a hematologic DLT, the dose of lenalidomide may be reintroduced to the next higher dose level (up to the starting dose) at the discretion of the treating physician if continued lenalidomide / dexamethasone therapy resulted in improved bone marrow function (no DLT for at least 2 consecutive cycles and an ANC ≥ 1,500/µL with a platelet count ≥ 100,000/µL at the beginning of a new cycle at the current dose level).

<u>All patients</u>
For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has

resolved to ≤ grade 2 depending on the physician's discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is suspected, and should not be resumed following discontinuation from these reactions.

Special populations

Paediatric population
Revlimid should not be used in children and adolescents from birth to less than 18 years because of safety concerns (see section 4.4).

Older people
Currently available pharmacokinetic data are described in section 5.2. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 91 years of age (see section 5.1).

In patients with newly diagnosed multiple myeloma aged 75 years and older who received lenalidomide, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation (see section 4.4). Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered (see section 4.4).

- *Newly diagnosed multiple myeloma*

For patients older than 75 years of age treated with lenalidomide in combination with dexamethasone, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. In clinical trials of newly diagnosed multiple myeloma in transplant non eligible patients, lenalidomide combined therapy was less tolerated in the patients older than 75 years of age compared to the younger population. These patients discontinued at a higher rate due to intolerance (Grade 3 or 4 adverse events and serious adverse events), when compared to patients < 75 years. (see Section 4.4).

Patients with renal impairment
Lenalidomide is substantially excreted by the kidney; patients with greater degrees of renal impairment can have impaired treatment tolerance (see section 4.4). Care should be taken in dose selection and monitoring of renal function is advised.

No dose adjustments are required for patients with mild renal impairment. The following dose adjustments are recommended at the start of therapy and

throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease. There are no Phase III trial experiences with End Stage Renal Disease (ESRD) (CLcr < 30 ml/min, requiring dialysis).

- *Multiple myeloma*

Renal function (CLcr)	*Dose adjustment (Days 1 to 21 of repeated 28-day cycles)*
Moderate renal impairment (30 ≤ CLcr < 50 mL/min)	*10 mg once daily*[1]
Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis)	*15 mg every other day*
End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis)	*5 mg once daily. On dialysis days, the dose should be administered following dialysis.*

[1] *The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.*

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.

<u>Patients with hepatic impairment</u>
Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

<u>Method of administration</u>
Oral use.

Revlimid® capsules should be taken at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

2.	2.1 **Binocrit 2,000 IU/1 ml solution for injection in a pre-filled syringe** [Epoetin alpha 2,000 IU (Corresponding to 16.8 mcg epoetin alpha)] 2.2 **Binocrit 4,000 IU/0.4 ml solution for injection in a pre-filled syringe** [Epoetin alpha 4,000 IU (Corresponding to 33.6 mcg epoetin alpha)] 2.3 **Binocrit 10 000 IU/1 ml solution for injection in a pre-filled syringe** [Epoetin alpha 2,000 IU (Corresponding to 84.0 mcg epoetin alpha)] 2.4 **Binocrit 40, 000 IU/1 ml solution for injection in a pre-filled syringe** [Epoetin alpha 2,000 IU (Corresponding to 336.0 mcg epoetin alpha)]	➢ Posology: *<u>Additional route of administration:</u>* *Subcutaneous* *<u>Posology and method of administration</u>* *Treatment with Binocrit has to be initiated under the supervision of physicians experienced in the management of patients with the above indications.* *<u>Posology</u>* *<u>Treatment of symptomatic anaemia in adult and paediatric chronic renal failure patients:</u>* *In patients with chronic renal failure where intravenous access is routinely available (haemodialysis patients) administration of Binocrit by the intravenous route is preferable.* *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.* *The haemoglobin concentration aimed for is between 10 and 12 g/dl (6.2-7.5 mmol/l) in adults, and between 9.5 and 11 g/dl (5.9-6.8 mmol/l) in paediatric patients.* *A sustained haemoglobin level of greater than 12 g/dl (7.5 mmol/l) should be avoided. If the haemoglobin is rising by more than 2 g/dl (1.25 mmol/l) per month, or if the sustained haemoglobin exceeds 12 g/dl (7.5 mmol/l) reduce the epoetin alfa dose by 25%. If the haemoglobin exceeds 13 g/dl (8.1 mmol/l), discontinue therapy until it falls below 12 g/dl (7.5 mmol/l) and then reinstitute epoetin alfa therapy at a dose 25% below the previous level.* *Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed.* *Patients should be monitored closely to ensure that the lowest approved dose of epoetin alfa is used to provide adequate control of anaemia and of the symptoms of anaemia.* *Iron status should be evaluated prior to and during treatment and iron supplementation administered if necessary. In addition, other causes of anaemia, such as vitamin B12 or folate deficiency, should be excluded before instituting therapy with epoetin alfa. Non response to epoetin alfa therapy may have the following causes: iron, folate or vitamin B12 deficiency; aluminium intoxication; intercurrent infections; inflammatory or traumatic episodes; occult blood loss;*	**NOVARTIS CORPORATION (MALAYSIA) SDN. BHD.** Level 22, Tower B, Plaza 33 No. 1, Jalan Kemajuan, Seksyen 13 46200 Petaling Jaya, Selangor

		haemolysis, and bone marrow fibrosis of any origin. *Adult haemodialysis patients:* *In patients on haemodialysis where intravenous access is routinely available, administration by the intravenous route is preferable.* *The treatment is divided into two stages:* *Correction phase:* *50 IU/kg 3 times per week. When a dose adjustment is necessary, this should be done in steps of at least four weeks. At each step, the increase or reduction in dose should be of 25 IU/kg 3 times per week.* *Maintenance phase:* *Dose adjustment in order to maintain haemoglobin values at the desired level: Hb between 10 and 12 g/dl (6.2-7.5 mmol/l).* *The recommended total weekly dose is between 75 and 300 IU/kg which is administered in dosed of 25-100 IU/kg three times per week. The clinical data available suggest that those patients whose initial haemoglobin is very low (<6 g/dl or <3.75 mmol/l) may require higher maintenance doses than those whose initial anaemia is less severe (Hb >8 g/dl or >5 mmol/l).* *Paediatric haemodialysis patients:* *In paediatric patients on haemodialysis where intravenous access is routinely available, administration by the intravenous route is preferable.* *The treatment is divided into two stages:* *Correction phase:* *50 IU/kg 3 times per week. When a dose adjustment is necessary, this should be done in steps of 25 IU/kg 3 times per week at intervals of at least 4 weeks until the desired goal is achieved.* *Maintenance phase:* *Dose adjustment in order to maintain haemoglobin values at the desired level: Hb between 9.5 and 11 g/dl (5.9-6.8 mmol/l).* *Generally, children under 30 kg require higher maintenance doses than children over 30 kg and adults.* *The following maintenance doses were observed in clinical trials after 6 months of treatment:*	

Weight (kg)	Dose (IU/kg given 3x/week)	
	Median	Usual maintenance does
< 10	100	75 - 150
10 – 30	75	60 - 150
>30	33	30 – 100

The clinical data available suggest that those paediatric patients whose initial haemoglobin is very low (<6.8 g/dl or <4.25 mmol/l) may require higher maintenance doses than those whose initial anaemia is less severe (Hb>6.8 g/dl or >4.25 mmol/l).

Adult peritoneal dialysis patients:
The treatment is divided into two stages:
When intravenous access is not readily available Binocrit may be administered subcutaneously.

Correction phase:
Starting dose of 50 IU/kg twice a week.

Maintenance phase:
Dose adjustment in order to maintain haemoglobin values at the desired level: Hb between 10 and 12 g/dl (6.2-7.5 mmol/l). Maintenance dose between 25 and 50IU/kg twice a week into 2 equal injections.

Adult patients with renal insufficiency not yet undergoing dialysis:
Where intravenous access is not readily available Binocrit may be administered subcutaneously.

The treatment is divided into two stages:

Correction phase:
Starting dose of 50 IU/kg 3 times per week, followed if necessary by a dose increase with 25 IU/kg increments (3 times per week) until the desired goal is achieved (this should be done in steps of at least four weeks).

Maintenance phase:
During the maintenance phase, Binocrit can be administered either 3 times per week, and in the case of subcutaneous administration, once weekly or once every 2 weeks.

Dose adjustment in order to maintain haemoglobin values at the desired level: Hb between 10 and 12 g/dl (6.2-7.5 mmol/l). Maintenance dose between 17 and 33IU/kg 3 times per week by the intravenous route.

The maximum dose should not exceed 150 IU/kg 3 times per week,240 IU/kg (up to a maximum of 20000 IU) once weekly, or 480 IU/kg (up to a maximum of 40000 IU) once every 2 weeks.

Anaemia in chronic renal failure patients before initiation of dialysis or on peritoneal dialysis:
The safety and efficacy of epoetin alfa in chronic renal failure patients with anaemia before initiation of dialysis or on peritoneal dialysis have not been established. Currently available data for the subcutaneous use of epoetin alfa in these populations are described in section pharmacodynamic properties but no recommendation on posology can be made.
Treatment of patients with chemotherapy induced anaemia:
Epoetin alfa should be administered by the subcutaneous route to patients with anaemia (e.g. haemoglobin concentration ≤10 g/dl (6.2 mmol/l). Anaemia symptoms and sequelae may vary with age, gender and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary.

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management with consideration for the haemoglobin target range of 10 g/dl (6.2 mmol/l) to 12 g/dl (7.5 mmol/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 (7.5 mmol/l) are observed are described below.

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

Epoetin alfa therapy should be continued until one month after the end of chemotherapy.

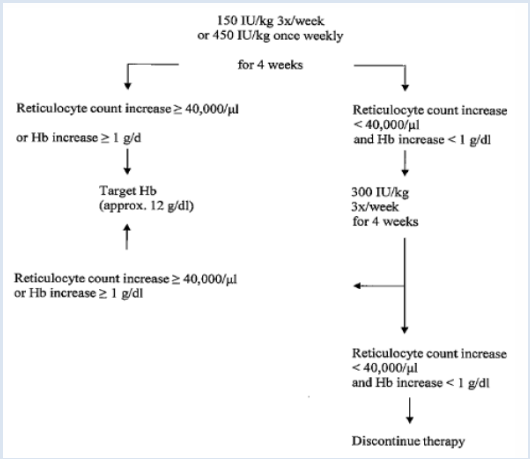
The initial dose is 150 IU/kg given subcutaneously 3 times per week. Alternatively, epoetin alfa can be administered at an initial dose of 450 IU/kg subcutaneously once weekly.

- *If haemoglobin has increased by at least 1 g/dl (>0.62 mmol/l) or the reticulocyte count has increased ≥40,000 cells/µl above baseline after 4 weeks of treatment, the dose should remain at 150 IU/kg 3 times a week or 450 IU/kg once weekly.*
- *If the haemoglobin increase is <1 g/dl (<0.62 mmol/l) and the reticulocyte count has increased <40,000 cells/µl above baseline, increase the dose to 300 IU/kg 3 times per week. If after an additional 4 weeks of therapy at 300 IU/kg 3 times per week, the haemoglobin has increased ≥1 g/dl (>0.62*

mmol/l) or the reticulocyte count has increased ≥40,000 cells/µl, the dose should remain at 300 IU/kg 3 times per week.

However, if the haemoglobin has increased <1 g/dl (<0.62 mmol/l) and the reticulocyte count has increased <40,000 cells/µl above baseline, response to epoetin alfa therapy is unlikely and treatment should be discontinued.

The recommended dosing regimen is described in the following diagram:



Dosage adjustment to maintain haemoglobin concentration between 10 g/dl – 12 g/dl (6.2 mmol/l - 7.5 mmol/l):

If the haemoglobin is rising by more than 2 g/dl (1.25 mmol/l) per month, or if the haemoglobin exceeds 12 g/dl (7.5 mmol/l), the dose should be reduced by approximately 25 to 50%. If the haemoglobin exceeds 13 g/dl (8.1 mmol/l), discontinue therapy until it falls below 12 g/dl (7.5 mmol/l) and then reinstitute epoetin alfa therapy at a dose 25% below the previous dose.

Adult surgery patients in an autologous predonation programme:
Binocorit should be given by the intravenous route.

At the time of donating blood, Binocrit should be administered after the completion of the blood donation procedure.

Mildly anaemic patients (haematocrit of 33-39%) requiring predeposit of ≥4 units of blood should be treated with Binocrit at a dose of 600 IU/kg body weight twice a week for 3 weeks prior to surgery.

All patients being treated with Binocrit should receive adequate iron

supplementation (e.g. 200 mg oral elemental iron daily) throughout the course of treatment. Iron supplementation should be started as soon as possible, even several weeks prior to initiating the autologous predeposit, in order to achieve high iron stores prior to starting Binocrit therapy.

<u>Treatment of adult patients scheduled for major elective orthopaedic surgery:</u>
The subcutaneous route of administration should be used.

The recommended dose is 600 IU/kg epoetin alfa, given once a week for three weeks (day 21, 14 and 7) prior to surgery and on the day of surgery (day 0). In cases where there is a medical need to shorten the lead time before surgery to less than three weeks, 300 IU/kg epoetin alfa should be given daily for 10 consecutive days prior to surgery, on the day of surgery and for four days immediately thereafter. When performing haematologic assessments during the preoperative period, if the haemoglobin level reaches 15 g/dl (9.38 mmol/l), or higher, administration of epoetin alfa should be stopped and further doses should not be given.

Care should be taken to ensure that at the outset of the treatment patients are not iron deficient.

All patients being treated with epoetin alfa should receive adequate iron supplementation (e.g. oral iron substitution of 200 mg Fe2+ daily) throughout the course of epoetin alfa treatment. Iron supplementation should be started prior to epoetin alfa therapy, to achieve adequate iron stores.

<u>Method of administration</u>
Binocrit is a sterile but unpreserved product and is for single use only. Administer the amount required. This medicinal product must not be administered by intravenous infusion, or mixed with other medicinal products.

1. *Intravenous injection: over at least one to five minutes, depending on the total dose. In haemodialysed patients, a bolus injection may be given during the dialysis session through a suitable venous port in the dialysis line. Alternatively, the injection can be given at the end of the dialysis session via the fistula needle tubing, followed by 10 ml of isotonic saline to rinse the tubing and ensure satisfactory injection of the product into the circulation. A slower injection is preferable in patients who react to the treatment with 'flu-like symptoms'.*
2. *Subcutaneous injection: a maximum volume of 1 ml at one injection site should generally not be exceeded. In case of larger volumes, more than one site should be chosen for injection. The injections are given in the thighs or the anterior abdomen wall.*