HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 December 2007

MIRCERA 50 µg/0.3 mL, solution for injection
Box containing one pre-filled syringe (CIP: 381 514-5)

MIRCERA 75 µg/0.3 mL, solution for injection
Box containing one pre-filled syringe (CIP: 381 515-1)

MIRCERA 100 µg/0.3 mL, solution for injection
Box containing one pre-filled syringe (CIP: 381 517-4)

MIRCERA 150 µg/0.3 mL, solution for injection
Box containing one pre-filled syringe (CIP: 381 518-0)

MIRCERA 200 µg/0.3 mL, solution for injection
Box containing one pre-filled syringe (CIP: 381 520-5)

MIRCERA 250 µg/0.3 mL, solution for injection
Box containing one pre-filled syringe (CIP: 381 521-1)

Applicant: ROCHE

Methoxy polyethylene glycol-epoetin beta

ATC Code: B03XA03

List I

Medicinal product requiring an initial annual hospital prescription exclusively by nephrology, haematology or internal medicine specialists

Date of Marketing Authorisation: 20 July 2007 (centralised procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Methoxy polyethylene glycol-epoetin beta

1.2. Indication

"Treatment of anaemia associated with chronic kidney disease (CKD).
The safety and efficacy of MIRCERA in other indications have not been established."

1.3. Dosage

Treatment with MIRCERA has to be initiated under the supervision of a physician experienced in the management of patients with renal impairment.

The solution can be administered subcutaneously or intravenously. MIRCERA can be injected subcutaneously in the abdomen, arm or thigh. All three injection sites are equally suitable.

It is recommended that haemoglobin is monitored every two weeks until stabilized and periodically thereafter.

Patients not currently treated with an erythropoiesis stimulating agent (ESA):

The recommended starting dose is 0.6 micrograms per kg body weight, administered once every two weeks as a single intravenous or subcutaneous injection in order to increase the haemoglobin to greater than 11 g/dl (6.83 mmol/l).

The dose may be increased by approximately 25% of the previous dose if the rate of rise in haemoglobin is less than 1.0 g/dl (0.621 mmol/l) over a month. Further increases of approximately 25% may be made at monthly intervals until the individual target haemoglobin level is obtained.

If the rate of rise in haemoglobin is greater than 2 g/dl (1.24 mmol/l) in one month or if the haemoglobin level is increasing and approaching 12 g/dl (7.45 mmol/l), the dose is to be reduced by approximately 25%. If the haemoglobin level continues to increase, therapy should be interrupted until the haemoglobin level begins to decrease, at which point therapy should be restarted at a dose approximately 25% below the previously administered dose. After dose interruption a haemoglobin decrease of approximately 0.35 g/dl per week is expected. Dose adjustments should not be made more frequently than once a month.

If the haemoglobin concentration above 11 g/dl (6.83 mmol/l) is reached for the individual patient, MIRCERA may be administered once monthly using the dose equal to twice the previous once every two weeks dose.

Patients currently treated with an ESA:

Patients currently treated with an ESA can be converted to MIRCERA administered once a month as a single intravenous or subcutaneous injection. The starting dose of methoxy polyethylene glycol-epoetin beta is based on the calculated previous weekly dose of darbepoetin alfa or epoetin at the time of substitution as described in Table 1. The first injection should start at the next scheduled dose of the previously administered darbepoetin alfa or epoetin.

Table 1: Starting doses of MIRCERA

Previous weekly darbepoetin alfa intravenous or subcutaneous dose (microgram/week)	Previous weekly epoetin intravenous or subcutaneous dose (IU/week)	Monthly MIRCERA intravenous or subcutaneous dose (microgram/once monthly)
< 40	< 8 000	120
40 – 80	8 000 – 16 000	200
> 80	> 16 000	360

If a dose adjustment is required to maintain the target haemoglobin concentration above 11 g/dl (6.83 mmol/l), the monthly dose may be increased by approximately 25%.

If the rate of rise in haemoglobin is greater than 2 g/dl (1.24 mmol/l) over a month or if the haemoglobin level is increasing and approaching 12 g/dl (7.45 mmol/l), the dose is to be reduced by approximately 25%. If the haemoglobin level continues to increase, therapy should be interrupted until the hemoglobin level begins to decrease, at which point therapy should be restarted at a dose approximately 25% below the previously administered dose. After dose interruption a haemoglobin decrease of approximately 0.35 g/dl per week is expected. Dose adjustments should not be made more frequently than once a month.

Since the treatment experience is limited in patients on peritoneal dialysis, regular Hb monitoring and strict adherence to dose adjustment guidance is recommended in these patients.

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 is to be administered as soon as possible and administration of MIRCERA is to be restarted at the prescribed dosing frequency.

Paediatric use
MIRCERA is not recommended for use in children and adolescents below 18 years due to a lack of safety and efficacy data.

Elderly patients
In clinical studies 24% of patients treated with MIRCERA were age 65 to 74 years, while 20% were age 75 years and over. No dose adjustment is required in patients aged 65 years or older.

Patients with hepatic failure
The safety and efficacy of MIRCERA therapy have not been established in patients with severe liver disease. Therefore, caution should be used in these patients.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

B Blood and haematopoietic organs
B03 Anti-anaemia preparations

B03X Other anti-anaemia preparations
B03XA Other anti-anaemia preparations
B03XA03 Methoxy polyethylene glycol-epoetin beta

2.2. Medicines in the same therapeutic category

2.2.1. Medicines that are strictly comparable

These are other erythopoiesis-stimulating agents indicated for the treatment of anaemia associated with chronic renal failure:

ARANESP : darbepoetin alfa
DYNEPO : epoetin delta
EPREX : epoetin alfa
NEORECORMON : epoetin beta

2.2.2. Medicines that are not strictly comparable

None

2.3. Medicines with a similar aim

Concentrated transfusions of red blood cells have the same therapeutic aim as MIRCERA.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The pharmaceutical firm submitted six phase III studies[1] to support its request:

- Two studies of anaemia correction and maintenance treatment in patients suffering from chronic kidney disease (CKD) who have never previously been treated with an erythropoiesis-stimulating agent (ESA):
  - AMICUS (BA16736) on patients receiving dialysis
  - ARCTOS (BA16738) on patients not receiving dialysis
- Four maintenance studies on patients with CKD who were receiving dialysis and had previously been treated with an ESA:
  - MAXIMA (BA16739)
  - PROTOS (BA16740)
  - STRIATA (BA17283)
  - RUBRA (BA17284)

[1] For details of these studies see the EPAR section of: http://www.ema.europa.eu

3.1.1. Studies of anaemia correction and maintenance treatment

Table 2 contains a summary of the protocols of the AMICUS and ARCTOS studies.

Table 2: Protocols of the AMICUS and ARCTOS studies

Study	AMICUS	ARCTOS
Primaryobjective	To demonstrate the efficacy of intravenous (IV) MIRCERA in correcting anaemia in patients with CKD who are receiving dialysis and are not being treated with an ESA.	To demonstrate the efficacy of subcutaneous (SC) MIRCERA in correcting anaemia in patients with CKD who are not receiving dialysis and were not being treated with an ESA prior to the study.
Method	Non-comparative, randomised, open-label study with an epoetin alpha arm on epoetin beta arm (internal validity of the study).	Randomised, open-label comparative study versus darbepoetin alfa.
Study design	- Correction phase: 24 weeks with the target of a haemoglobin (Hb) level ≥ 11g/dL and an increase of ≥ 1g/dL compared to the starting Hb level. - Evaluation: after 24 weeks. - Maintenance phase: 28 weeks. Randomisation of patients on MPG-epoetin beta who have achieved the target of the treatment into two dosage groups	- Correction phase: 28 weeks with the target of an Hb level ≥ 11g/dL and an increase of ≥ 1g/dL compared to the starting Hb level. - Evaluation phase: last 10 weeks of the correction phase. - Maintenance phase: 24 weeks. Randomisation of patients on MPG-epoetin beta who have achieved the target of the treatment into two dosage groups.
Inclusion criteria	Adult patients with CKD stage 5, on dialysis and not receiving any erythropoiesis-stimulating treatment before the study. Iron status: serum ferritin levels ≥ 100 ng/mL or transferrin saturation ≥ 20% (or hypochromic red cells <10%). Hb level before dialysis: 8-11 g/dL. Haemodialysis or peritoneal dialysis for at least two weeks prior to selection.	Adult patients with CKD stage 3/4, not on dialysis and not receiving any erythropoiesis-stimulating treatment before the study. Iron status: serum ferritin levels ≥ 100 ng/mL or transferrin saturation ≥ 20% (or hypochromic red cells <10%). Hb level: 8-11 g/dL.
Treatments	▪ **MPG-epoetin beta*:** - Correction: initial dose of 0.4 µg/kg 1x/2 weeks Target Hb concentration: ≥ 11g/dL and an increase of ≥ 1g/dL compared to the starting level. Dose adjustment every four weeks if the patient does not respond adequately to treatment. - Maintenance: for patients who have achieved the target of the treatment, randomisation into 2 groups: 1x/2 weeks and 1x/4 weeks. Dose adjustment to maintain Hb concentrations between 11.0 and 13.0 g/dL. ▪ **Epoetin alpha or beta:** 3x/week by IV administration, according to the dosage laid down in the MA, throughout the study.	▪ **MPG-epoetin beta:** - Correction: initial dose of 0.6 µg/kg 1x/2 weeks Target Hb concentration: ≥ 11g/dL and an increase of ≥ 1g/dL compared to the starting level. Dose adjustment every four weeks if the patient does not respond adequately to treatment. - Maintenance: for patients who have achieved the target of the treatment, randomisation into 2 groups: 1x/2 weeks and 1x/4 weeks. Dose adjustment to maintain Hb concentrations between 11.0 and 13.0 g/dL. ▪ **Darbepoetin alpha:** 1x/week by SC administration according to the dosage laid down in the MA during the correction and evaluation phases, then 1x/2 weeks during the maintenance phase.
Primary endpoints	% of patients responding during the correction phase (24 weeks) with an Hb level ≥ 11g/dL and an increase of ≥ 1g/dL compared to the starting level (Hb levels measured once a week), with no red blood cells transfusion prior to the response, during the 24 weeks after the first dose.	- % of patients responding during the correction phase (28 weeks) with an Hb level ≥ 11g/dL and an increase of ≥ 1g/dL compared to the starting level. - Change in the average Hb level between the evaluation phase and the starting Hb level.

*** :** methoxy polyethylene glycol-epoetin beta

Statistical analysis:

- AMICUS study:
The primary analysis is focused on the assessment of the efficacy of MPG-epoetin beta in terms of the percentage of responders. The treatment was to be regarded as effective if the lower limit of the 95% confidence interval of the percentage of responders was equal to or greater than 60%. The purpose of the comparator arm was to verify whether the efficacy level of MPG-epoetin beta was similar to that of a comparator. The analysis was performed on the intention-to-treat (ITT) population.
No statistical comparison between MPG-epoetin beta and the epoetin alpha or beta was planned by the protocol of this study .

- ARCTOS study:
The primary analysis focused on the assessment of the efficacy of MPG-epoetin beta in terms of the percentage of responders, according to the same criteria as those used in the AMICUS study (see paragraph above).
A secondary analysis tested the hypothesis of the non-inferiority of MPG-epoetin beta to darbepoetin alfa according to the change in the average Hb level compared to the starting Hb level. A covariance analysis (ANCOVA) was used to compare the two groups: in this model, the independent variable was the treatment group and the covariables were the Hb level and the geographical area. MPG-epoetin beta was to be considered as not inferior to darbepoetin if the lower limit of the 95% confidence interval of the difference between the treatments was greater than or equal to -0.75 g/dL. The difference between the treatments should not exceed 0.3 g/dL and the proportion of per--protocol patients ineligible should not exceed 20%. The analysis was performed on the per-protocol (PP) and intention-to-treat (ITT) populations.
The hierarchical structure of the tests ensured that the risk of incorrectly concluding that there was a significant difference did not exceed 5%.

Results:

- AMICUS study:
A total of 181 patients (out of 234 initially selected) were randomised into the MPG-epoetin beta (n=135) and epoetin (n=46) groups.
One hundred and twenty four patients in the MPG-epoetin beta group and 41 in the epoetin group completed the correction phase.
The mean age of all the patients in the study was 54. The mean Hb level at inclusion was 9.4 g/dL in both groups. Ninety eight percents of the patients in the MPG-epoetin group were on haemodialysis, as 100% of the epoetin group.

The percentage of responders was 93.3% (95% CI = [87.7 ; 96.9]) in the MPG-epoetin beta group and 91.3% in the epoetin group (95% CI = [79.2 ; 97.6]). The lower limit of the 95% confidence interval was above 60% in both groups. Therefore, both treatments could be regarded as effective in patients suffering from CKd who were on dialysis and had never previously received an ESA treatment.

- ARCTOS study:
A total of 324 patients (out of 496 initially selected) were randomised into the MPG-epoetin beta (n=162) and darbepoetin (n=162) groups. One hundred and fifty one patients in the MPG-epoetin beta group and 158 in the darbepoetin group completed the correction and evaluation phases.
The mean age of all the patients in the study was 65 years old. The mean Hb level at inclusion was 10.2 g/dL in both groups.

The percentage of responders was 97.5% (95% CI = [93.8 ; 99.3]) in the MPG-epoetin beta group and 96.3% in the darbepoetin group (95% CI = [92.1 ; 98.6]). The lower limit of the 95% confidence interval (CI) was above 60% in both groups. Therefore, both treatments

could be regarded as effective in patients suffering from CRF who were not on dialysis and had never previously received an ESA treatment.

The adjusted mean change in the Hb level compared to the Hb level at inclusion was 2.15 g/dL in the MPG-epoetin beta group and 1.99 g/dL in the darbepoetin group (a difference of 0.155 g/dL), with a 95% confidence interval of [-0.045 ; 0.354] (PP population).
As the lower limit of the 95% confidence interval of the difference between the treatments was greater than -0.75 g/dL, which had been defined as the non-inferiority threshold, it can be concluded that MPG-epoetin beta is not inferior to darbepoetin in a population of patients suffering from CKd who are not on dialysis and have never previously received an ESA treatment (result confirmed in the ITT population).

Conclusion:
Both studies showed MPG-epoetin beta, administered by SC or IV route once every two weeks, to be effective in correcting anaemia in patients suffering from CKD, irrespective of whether or not they are on dialysis, and who have never previously received an ESA treatment.
Furthermore, MPG-epoetin beta was not inferior to darbepoetin in respect of the average change in the Hb level after 28 weeks of SC treatment once every two weeks in patients suffering from CKD who were not on dialysis and who had never previously received treatment (one study).

3.1.2. Maintenance treatment studies

The protocols for the MAXIMA, PROTOS, STRIATA and RUBRA studies were similar.

Primary objective: To assess the efficacy of MPG-epoetin beta on Hb level maintenance in patients with CKD, on dialysis, previously treated with ESA, in comparison to the efficacy of other ESAs.

Method: Randomised, open-label controlled studies versus active comparator.

Study design:
Three-phase efficacy assessment:
- patient selection : 4 weeks
- dose adjustment : 28 weeks
- efficacy assessment : 8 weeks

In the MAXIMA, PROTOS and STRIATA studies, treatment continued for a further 16 weeks in order to monitor tolerance.

Main inclusion criteria:
Adult patients with CKD, on dialysis, previously treated with an ESA. The patients were required to have been on haemodialysis or peritoneal dialysis (same mode) for at least twelve months, to have an Hb level between 10.5 and 13 g/dL, an iron status defined by serum ferritin levels ≥ 100 ng/mL or transferrin saturation ≥ 20% (or percentage of hypochromic red cells <10%).

Treatments and patient numbers: see table 3.

Table 3: Treatments and numbers of patients in each group in the maintenance treatment studies

Study	MPG-epoetin beta			Comparator			
	Dosage	Route	No. of patients	ESA	Dosage	Route	No. of patients
MAXIMA	1x/2 weeks 1x/4 weeks	IV IV	223 224	Epoetin α and β	1 to 3x a week	IV	226
PROTOS	1x/2 weeks 1x/4 weeks	SC SC	190 191	Epoetin α and β	1 to 3x a week	SC	191
STRIATA	1x/2 weeks	IV	157	Darbepoetin α	Once a week or 1x/2 weeks	IV	156
RUBRA*	1x/2 weeks	IV or SC	168	Epoetin α and β	1 to 3x a week	IV or SC	168

* : MPG-epoetin beta in prefilled syringe

In the four studies, the patients in the MPG-epoetin beta group were given an initial dose calculated on the basis of the weekly dose of epoetin or darbepoetin alfa administered in the week before the change.
The doses were adjusted in order to maintain an Hb level of ±1.0 g/dL compared to Hb level at the time of selection and between 10.0 and 13.5 g/dL throughout the dose adjustment and the efficacy assessment periods. The dose adjustments could not take place more than once a month.

Primary endpoint:
Change in the mean Hb level between the evaluation period and the selection period.

Statistical analysis:
The hypothesis of the non-inferiority of MPG-epoetin beta to other ESAs was tested according to the change in the mean Hb level compared to the starting HB level. A covariance analysis (ANCOVA) was used to compare the groups: in this model, the independent variable was the treatment group and the covariables were the initial Hb level and the geographical area. MPG-epoetin beta was to be considered as not inferior to its comparator if the lower limit of the 95% confidence interval (STRIATA and RUBRA studies) or the 97.5% confidence interval (MAXIMA and PROTOS studies) of the difference between the treatments was greater than or equal to -0.75 g/dL. The difference between the treatments should not exceed 0.3 g/dL and the proportion of per--protocol patients ineligible should not exceed 20%. The analysis was performed on the per-protocol (PP) and intention-to-treat (ITT) populations.

Results:
Populations included in the studies: see table 4

Table 4: Numbers of patients taking part in maintenance treatment studies

Studies	Number of patients randomised	Number of patients after the dose adjustment phase	Number of patients after the efficacy assessment phase
MAXIMA			
MPG-epoetin 1x/2 weeks	223	197	190
MPG-epoetin 1x/4 weeks	224	188	183
Epoetin α and β	226	205	199
PROTOS			
MPG-epoetin 1x/2 weeks	190	164	161
MPG-epoetin 1x/4 weeks	191	170	166
Epoetin α and β	191	181	175
STRIATA			
MPG-epoetin 1x/2 weeks	157	139	130
Darbepoetin α	156	143	136
RUBRA			

MPG-epoetin 1x/2 weeks	168	146	132
Epoetin α and β	168	160	150

The baseline Hb levels in all studies ranged from 11.7 to 12.0 g/dL. Most patients had received or were continuing to receive iron supplementation: 77 to 81% in the MAXIMA study, 81 to 84% in the PROTOS study, 83 to 85% in the STRIATA study. In the RUBRA study, 72% of patients in the MPG-epoetin group and 63% of patients in the comparator group had been received or were continuing to receive iron supplementation. The median transferrin saturation (TSAT) rate was between 27 and 31% in all the studies.

All four studies found MPG-epoetin to be non-inferior to the other ESAs in respect of the change in the mean Hb rate between the efficacy assessment phase and the starting Hb level (see table 5).

Table 5: Results of maintenance treatment studies: change in the adjusted mean Hb level between the efficacy assessment phase and the initial Hb level (per-protocol population, non-inferiority threshold of - 0.75 g/dL)

Study	Treatments	Change in average Hb level	Difference MPG-epoetin vs. comparator	95%CI
MAXIMA	MPG-epoetin β 1x/2 weeks MPG-epoetin β 1x/4 weeks Epoetin α or β	- 0.025 (n=172) - 0.071 (n=188) - 0.075 (n=180)	0.051 0.004 -	[-0.173 ; 0.275] [-0.215 ; 0.223
PROTOS	MPG-epoetin β 1x/2 weeks MPG-epoetin β 1x/4 weeks Epoetin α or β	- 0.131 (n=153) 0.032 (n=154) - 0.109 (n=167)	- 0.022 0.141 -	[-0.262 ; 0.217] [-0.098 ; 0.380]
STRIATA	MPG-epoetin β 1x/2 weeks Darbepoetin	0.063 (n=123) - 0.116 (n=126)	0.180 -	[-0.049 ; 0.408]
RUBRA	MPG-epoetin β 1x/2 weeks Epoetin α or β	0.088 (n=123) - 0.030 (n=133)	0.118 -	[-0.116 ; 0.353]

3.2. Adverse effects

Safety data were collected from four phase II dose studies and six phase III studies. A total of 2,737 patients took part in these studies; 1,789 were treated with MPG-epoetin and 948 with another ESA. A pooled analysis of these data was performed.

The safety profiles of MPG-epoetin and the other ESAs were similar. The adverse events most frequently reported were hypertension, diarrhoea, headache and rhinopharyngeal infections.

The results showed the incidence of adverse events associated with treatment to be 7% in the MPG-epoetin group and 5% in the comparator ESA group. The adverse event associated with treatment most frequently observed was hypertension (27/1,789, i.e. 1.51% in the MPG epoetin group and 14/948, i.e.1.48% in the comparator group). Overall, there was no difference in the rate of vascular events associated with treatment between MPG-epoetin and the comparators (2%).

Nine cases of pulmonary embolism among the 1 789 patients (0.5%) in the MPG-epoetin group were observed in the MPG-epoetin group, compared to none with the comparators. The investigator was of the opinion that these cases were not related to the treatment.

Serious gastrointestinal haemorrhage was observed more often in patients taking MPG-epoetin than in patients taking comparators (21/1,789, i.e. 1.2% vs. 2/1,789, i.e. 0.2%), while the frequency of all severe haemorrhagic events observed was the same. Furthermore, a slight decrease in platelet counts (remaining within the normal range) was also observed in patients being treated with MPG-epoetin beta. A platelet count of less than or equal to 100 x 10^9/L was observed in 7% of patients treated with MPG-epoetin beta and 4% of those treated with other ESAs.

The European Risk Management Plan indicates that patients should be monitored to ascertain the incidence of thromboembolic events, including pulmonary events, and gastrointestinal haemorrhage.

So far, none of the patients treated with MPG-epoetin beta in clinical studies has developed anti-erythropoietin antibodies.

No long-term safety data (beyond two years) assessing the risks associated with prolonged stimulation of erythrocyte precursors (in particular the risk of uncontrolled growth) were available. Longer-term safety results, arising from the 104-week extension of the phase II and III studies, were expected.

3.3. Conclusion

The efficacy of MPG-epoetin beta has been assessed in six randomised, open-label controlled phase III studies versus other ESAs (epoetin alfa and beta, darbepoetin alfa).

The AMICUS and ARCTOS studies were performed on ESA naive patients suffering from CKD. The aim of these studies was to correct haemoglobinaemia to achieve an Hb level of ≥11g/dL and an increase of ≥ 1g/dL compared to the starting Hb level (definition of a responsive patient) for 24 weeks in the AMICUS study and 28 weeks in the ARCTOS study.

The MAXIMA, PROTOS, STRIATA and RUBRA studies were performed on patients with CKD who had previously undergone ESA treatment. After a dose-adjustment phase of 28 weeks, the change in the mean Hb level was assessed over the course of eight weeks.
Some studies involved administration of MPG-epoetin beta by SC route while in others it was administered by IV route. The frequency of administration was one injection either every two weeks or every four weeks. The dose was adjusted every four weeks if the response to treatment was inadequate.

SC or IV administration of MPG-epoetin beta once every two weeks was effective in correcting haemoglobinaemia in ESA naive patients. The percentage of responders was 93.3% (95% CI = [87.7 ; 96.9]) *versus* 91.3% with epoetin alpha or beta (95% CI = [79.2 ; 97.6]) in the AMICUS study (patients on dialysis) and 97.5% (95% CI = [93.8 ; 99.3]) *versus* 96.3% with darbepoetin alpha (95% CI = [92.1 ; 98.6] in the ARCTOS study (patients not on dialysis). Furthermore, in this second study MPG-epoetin beta was found to be non-inferior to darbepoetin alpha in respect of the average change in the Hb level between the assessment phase and the starting Hb level.

In maintenance treatment of patients previously treated with ESA, following a dose-adjustment phase, MPG-epoetin beta administered by the SC or IV route once every two or four weeks was non-inferior to the other ESAs in respect of the change in the Hb level between the assessment phase and the starting level.

The safety data derived from all the phase II and phase III studies showed that the MPG-epoetin safety profile was similar to that of the other ESAs. The most frequent adverse events related to the treatment were hypertension (≥1/100 to <1/10). However, some differences were observed: pulmonary embolisms and gastrointestinal haemorrhage were more frequent in patients receiving MPG-epoetin than in patients receiving comparator substances (nine cases of pulmonary embolism in 1,789 patients taking MPG-epoetin and none in the patients taking the comparators). The European Risk Management Plan indicates that patients should be monitored concerning the incidence of these adverse events. Long-term safety results (104-week extension of the phase II and III studies) were expected.

In conclusion, MPG-epoetin beta was as effective as the other ESAs, and had a similar safety profile. However, there is still some uncertainty about safety over a longer term:

cardiovascular and haemorrhagic risks and the risk related to prolonged stimulation of erythropoietin receptors and erythrocyte precursors.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Chronic kidney disease is defined by a permanent decline in the glomerular filtration rate which has existed for at least three months. This parameter reflects the kidneys' filtration capacity. Chronic kidney disease is responsible for anaemia, which worsens as the severity of kidney disease increases. Anaemia is associated with an increase in the risk of mortality, morbidity and hospitalisation. It also has a negative impact on patients' quality of life. Dialysis or transplant must be considered for patients with terminal CRF, i.e. a filtration rate below 15 mL/min/1.73m^2.

This proprietary drug is intended to provide curative treatment.

Public health benefit:

The frequency and gravity of chronic kidney disease and the associated anaemia lead to a moderate public health burden of this condition.

Improving the management of anaemia associated with chronic kidney disease is a public health need that forms part of an established priority (GTNDO priority[2]: Improving the quality of life of patients with chronic renal failure).

However, the therapeutic need may be considered to be covered already by existing erythropoiesis-stimulating agents.
In view of the data available (in particular, insufficient quality of life data), MIRCERA is not expected to have any additional impact on morbidity or patients' quality of life despite the fact that it is more convenient (injections given at less frequent intervals than existing erythropoiesis-stimulating agents).

Furthermore, the results of these studies may not be transposable into practice given the uncertainty as to how well MIRCERA is tolerated (cardiovascular complications in particular), its very long half-life (it may prove difficult to monitor for any over-correction of haemoglobin) and the effective duration of treatment.

Consequently, in the current state of knowledge, MIRCERA is not expected to have any public health benefit.

The efficacy/safety ratio is high.

This proprietary drug provides first-line therapy.

Pharmacological and non-pharmacological alternatives (transfusions) exist.

The actual benefit of MIRCERA is substantial.

4.2. Improvement in actual benefit

MIRCERA offers no improvement in actual benefit (level V) compared to the other erythropoiesis-stimulating agents that are indicated in the correction of anaemia associated with chronic kidney disease.

[2] Groupe Technique National de Définition des Objectifs [National Technical Objective Definition Group] (DGS-2003)

4.3. Therapeutic use

4.3.1. Standard therapeutic strategy

The objective of the treatment is to improve survival and quality of life of patients and to reduce complications, especially cardiovascular ones.

In the case of all patients with chronic renal disease and a haemoglobin level of less than 11 g/dL, practitioners are advised to:
- investigate a non-renal cause for the anaemia, of which the primary one is iron deficiency;
- treat the iron deficiency if it exists;
- offer treatment with an ESA (erythropoietin alpha, beta or delta, or darbepoetin alpha) after ensuring absence of a curable cause of anaemia other than renal failure.

Clinical benefits of ESA have only been demonstrated in patients reaching a target haemoglobin level greater than 11 g/dL.
The benefits expected from prescription of an ESA are:
- a reduction in the prevalence of left ventricular hypertrophy once a target of more than 10 g/dl has been reached,
- improved quality of life,
- a decrease in transfusions and HLA hyperimmunisation, without an overall benefit in terms of renal transplantation.

ESA may be administered intravenously or subcutaneously.
The intravenous route is preferable for haemodialysed patients with respect to patient comfort.
In patients who are not haemodialysed, the ESA is preferably administered subcutaneously.
The dose administered should be individually adjusted so as to maintain the haemoglobin level within the target range of 10 to 12 g/dL.

Complementary treatments are: supplementation of iron, vitamins (C, B12, folic acid) and L-carnitine.

Transfusions should be avoided as far as possible in patients with chronic kidney disease and in patients awaiting transplantation (risk of alloimmunisation).

4.3.2. Medicinal product's therapeutic use

MIRCERA, methoxy polyethylene glycol-epoetin beta, is an additional ESA intended for use in managing anaemia in patients suffering from chronic kidney disease.

4.4. Target population

The target population for MIRCERA consists of patients with chronic kidney disease and anaemia. This population includes:
- patients on dialysis
- patients not yet on dialysis.

The population may be estimated from the following data[3]:
- In France, 30,000 patients[4] are on dialysis and 90% of them (expert opinion) have anaemia qualifying for treatment with erythropoietin.

[3] BEH – L'insuffisance rénale chronique [Chronic kidney disease] – 27 September 2005

- 6,500 and 7,500 patients[5] are at the pre-dialysis stage, 42%[6] of them received erythropoietin before their first dialysis.

On the basis of this data, the target population of MIRCERA may be estimated to be approximately 30,000 patients per year, with 27,000 on dialysis and 2,700 to 3,150 in the pre-dialysis stage.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indications and at the posology in the Marketing Authorisation.

The Transparency Committee suggests that a study be set up to monitor patients (with kidney disease) being treated by MIRCERA in France, with the aim of collecting the following factors under real treatment conditions:

- the conditions under which this treatment is used, including:
  - the clinical characteristics of patients undergoing treatment (whether or not they are on dialysis, reason for their kidney disease, confirmation that they are not suffering from iron or vitamin deficiency, etc.),
  - variations in the dosage of MIRCERA (dose, frequency of injections, duration of treatment) in the correction and maintenance phases,
  - details of how haemoglobinaemia and haematocrit levels are monitored;
- variations in haemoglobinaemia levels over the course of treatment and the occurrence of thromboembolic events;
- the frequency of treatment discontinuations and the reasons for them;
- impact on the quality of life of patients receiving treatment.

The duration of the study must be justified by an independent scientific committee.

The Transparency Committee suggests that:
- this monitoring study be carried out for all erythropoiesis-stimulating agents (ESAs) which have "kidney disease" as one of the indications listed in the Marketing Authorisation;
- data from the European Risk Management Plan be made available.

4.5.1. Packaging: Appropriate for the prescription conditions

4.5.2. Reimbursement rate: 65%

4.5.3. Exception drug status

The committee recommends awarding MIRCERA the status of a special exception drug. A prescription guide will specify the scope of reimbursement and the relevant dosage, along with the conditions for initiating treatment, monitoring patients and discontinuing treatment with MIRCERA.

[4] The prevalence of terminal chronic renal failure treated by dialysis in France in 2003: SROS-IRCT national survey

[5] Transparency Committee's opinion dated 24 January 2001 on the proprietary drugs EPREX and NEORECORMON, and opinion dated 5 September 2001 on the proprietary drug ARANESP

[6] Incidence and assessment of supplementation treatments for chronic renal failure in seven regions of France in 2003