HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 September 2012

SOLIRIS 300 mg, concentrate for solution for infusion
B/1 vial of 30 ml (10 mg/ml solution) (CIP code: 34009 571 1384 1)

Applicant: ALEXION PHARMA FRANCE

eculizumab

List I
Medicinal product reserved for hospital use. Prescription restricted to haematology, internal medicine, nephrology or paediatric specialists.
Orphan medicinal product.

Date of Marketing Authorisation: 21 June 2007 (centralised procedure)
Amendment of 24 November 2011: extension of the indication for the treatment of atypical haemolytic uremic syndrome

Reason for request: Inclusion on the list of medicines approved for hospital use in the extension of the indication to the treatment of atypical haemolytic uremic syndrome (aHUS).

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Eculizumab

1.2. Indication

"SOLIRIS (eculizumab) is indicated for the treatment of patients with:
- Paroxysmal nocturnal haemoglobinuria (PNH).

Evidence of clinical benefit of SOLIRIS in the treatment of patients with PNH is limited to patients with history of transfusions.
- **Atypical haemolytic uremic syndrome (aHUS)**."

1.3. Dosage

"SOLIRIS must be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological and/or renal disorders.

Dosage

In Paroxysmal Nocturnal Haemoglobinuria (PNH): *see SPC*

In Atypical Haemolytic Uremic Syndrome (aHUS):
The aHUS dosing regimen for adult patients (≥18 years of age) consists of a 4 week initial phase followed by a maintenance phase:

- Initial phase: 900 mg of SOLIRIS via a 25 – 45 minute intravenous infusion every week for the first 4 weeks,
- Maintenance phase: 1200 mg of SOLIRIS administered via a 25 – 45 minute intravenous infusion for the fifth week, followed by 1200 mg of SOLIRIS administered via a 25 – 45 minute intravenous infusion every 14 ± 2 days (see section 5.1[1]).

In paediatric aHUS patients (under 12 years) and adolescents (from 12 to 18 years), the SOLIRIS dosing regimen consists of:

Patient Body Weight	Initial Phase	Maintenance Phase
≥ 40 kg	900 mg / week over 4 weeks	1200 mg in 5th week then 1200 mg every 2 weeks
30 - <40 kg	600 mg / week over 2 weeks	900 mg in 3rd week then 900 mg every 2 weeks
20 - <30 kg	600 mg / week over 2 weeks	600 mg in 3rd week then 600 mg every 2 weeks
10 - <20 kg	600 mg / week for 1 week	300 mg in 2nd week then 300 mg every 2 weeks
5 - <10 kg	300 mg / week for 1 week	300 mg in 2nd week then 300 mg every 3 weeks

[1]of the SPC

Supplemental dosing of SOLIRIS is required in the setting of concomitant PE/PI (plasmapheresis or plasma exchange, or fresh frozen plasma infusion):

Type of intervention	Most recent SOLIRIS dose	Supplemental SOLIRIS Dose	Timing of Supplemental SOLIRIS Dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	≥ 600 mg	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	≥ 300 mg	300 mg per each unit of fresh frozen plasma	60 minutes prior to each 1 unit of fresh frozen plasma infusion

Method of administration

For instructions on dilution of the medicinal product before administration, see section 6.6.[1]

Do not administer as an intravenous push or bolus injection. SOLIRIS should only be administered via intravenous infusion as described below.

The diluted solution of SOLIRIS should be administered by intravenous infusion over 25 - 45 minutes via gravity feed, a syringe-type pump, or an infusion pump. It is not necessary to protect the diluted solution of SOLIRIS from light during administration to the patient.

Patients should be monitored for one hour following infusion. If an adverse event occurs during the administration of SOLIRIS, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time may not exceed two hours in adults and adolescents and four hours in children aged less than 12 years.

Paediatric population:
For PNH patients, no data is available for the paediatric population. For aHUS patients, the method of administration for SOLIRIS is the same whatever the age.

Elderly population: SOLIRIS may be administered to patients aged 65 years and over. There is no evidence to suggest that any special precautions are needed when older people are treated – although experience with SOLIRIS in this patient population is still limited.

Renal impairment: No dose adjustment is required for patients with renal impairment (see section 5.1[1]).

Hepatic impairment: The safety and efficacy of SOLIRIS have not been studied in patients with hepatic impairment.

Treatment monitoring

Patients with aHUS should be monitored for signs and symptoms of thrombotic microangiopathy (see section 4.4 Biological monitoring in aHUS).
SOLIRIS treatment is recommended to continue for the patient's lifetime, unless the discontinuation of SOLIRIS is clinically indicated (see section 4.4[1])."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

L : Antineoplastic and immunomodulating agents
L04 : Immunosuppressants
L04A : Immunosuppressants
L04AA : Selective immunosuppressants
L04AA25 : Eculizumab

2.2. Medicines in the same therapeutic category

There are no medicines in the same therapeutic category.

2.3. Medicines with a similar therapeutic aim

There are no other medicines with similar therapeutic aim.

Other aHUS treatments are plasma exchange (PE) or fresh frozen plasma infusion (FFPI).

3 ANALYSIS OF AVAILABLE DATA

The applicant has provided:
- two non-comparative phase II studies, evaluating the efficacy and safety of eculizumab in 20 patients (study C08-003) and 17 patients (study C08-002), adults and adolescents, with atypical HUS;
- a retrospective study of 30 patients (study C09-001r);
- 20 reported cases in the literature. Due to the rarity of the condition, these cases are being taken into consideration.

Atypical HUS is a very rare, severe, systemic genetic disease; it is a life-threatening condition encompassing thrombotic microangiopathy mediated through disruption of the alternative complement pathway. Its clinical expression is characterised by:
- mechanical anaemia with the presence of schistocytes,
- thrombocytopenia or reduction in platelet count,
- a systemic effect on the vital organs (an effect that can start in the kidneys with progress towards terminal renal, neurological, gastrointestinal and cardiovascular impairment).

3.1. Efficacy

3.1.1. Clinical studies C08-003 and C08-002

Aims of the trials:

Study C08-003 was carried out on adults/adolescent patients with atypical HUS, sensitive to plasmatherapy, with a stable platelet count and chronic renal impairment, treated with plasma exchange (PE) or fresh frozen plasma infusion (FFPI) for at least 8 weeks.
In these patients, treatment with eculizumab was expected to: control the process of systemic complement-mediated thrombotic microangiopathy, reduce or stop the need for PE or FFP infusions, stabilise or improve renal function and significantly increase quality of life.

Study C08-002 was carried out on adult/adolescent patients with atypical HUS resistant to plasmatherapy with progressive systemic thrombotic microangiopathy (lowered platelet count and elevated LDH levels) and impairment of vital organs (renal impairment).
For these patients, treatment with eculizumab was expected to: reduce thrombotic microangiopathy by inhibiting terminal complement activation, improve or preserve renal function, decrease or stop the need for PE or FFP infusions and improve haemolytic anaemia and quality of life.

Inclusion criteria:

Table 1: Inclusion criteria for studies C08-003 and C08-002

Study C08-003	**Study C08-002**
Male or female, age ≥ 12 years, weight ≥ 40 kg, with aHUS (diagnosis established by treating physician, initial presentation or complication, post-transplant or not)	
Patients receiving PE or FFP infusions (at least once every 2 weeks and a maximum of 3 times per week) over at least 8 weeks prior to the first dose of eculizumab	Low platelet count with at least 4 PE/FFP infusions in the week prior to screening
Stable platelet count	Low platelet count (<150x10^9/l or at least 25% below the mean count of the last three measurements, established during the last admission, in line with systemic thrombotic microangiopathy)
Haemolysis: LDH ≥ upper limit of normal (ULN)	
Renal impairment: creatinine ≥ ULN	
Effective contraception for women	
Informed consent from patient or their legal representative for adolescents	

Investigation or identification of a genetic mutation of complement factors was not required, nor was measurement of complement proteins or their activity. Patients could undergo dialysis during the studies.
All patients received a vaccination against *Neisseria meningitidis,* at least 14 days before the first dose of eculizumab, or in emergency situations, in combination with a prophylactic antibiotic therapy up to 14 days after the vaccination.

Main non-inclusion criteria:
- Thrombotic Thrombocytopenic purapura (TTP) (acquired or congenital form): ADAMTS13 activity < 5%,
- Previous history of cancer in the last 5 years,
- E. coli HUS producer of Shiga-like toxins,
- Known HIV infection,
- HUS linked to drug exposure,
- HUS linked to a bone marrow transplant,
- Untreated active systemic bacterial infection, which may affect the diagnosis or the treatment of aHUS,
- Unresolved meningococcal infection
- Pregnant/breast feeding,
- Known systemic lupus erythematosus,
- Confirmed sepsis (positives blood cultures in the 7 days following screening and not treated with effective antibiotic therapy),
- Treatment with IV immunoglobulin in the 8 weeks prior to screening, or with rituximab in the 12 weeks before, or with another immunosuppressant except in certain cases,
- Treatment with erythropoiesis stimulating agents, except if dose is stable during the 4 weeks prior to screening.

Patients on chronic dialysis were excluded from study C08-002.

Study design:
- Initial phase: 900 mg per week over 4 weeks following the last PE or FFP infusion,
- Week 5 (+/- 2 days): one dose of 1200 mg,
- Maintenance dose: 1200 mg every 14 days (+/- 2 days).

After Week 26, patients were able to extend their treatment with eculizumab within the context of a follow-up study.

Eculizumab was administered via IV infusion over 35 minutes.

Primary efficacy endpoints:

Table 2: Primary efficacy endpoints for studies C08-003 and C08-002

Study C08-003	Study C08-002
Reduction in thrombotic microangiopathy measured by the absence of signs of systemic thrombotic microangiopathy* over 26 weeks	Reduction in thrombotic microangiopathy measured by the progress in platelet count between the first dose of eculizumab and the end of the study (26 weeks)
Proportion of patients achieving haematological normalisation at 26 weeks (evaluated if the primary endpoint has been met)	

*Absence of signs of systemic thrombotic microangiopathy is defined by the absence of:
- reduction in platelet count above 25% compared with inclusion,
- treatment with PE or FFP infusions,
- new dialysis.

Haematological normalisation is defined as normalisation in platelet count and sustained LDH levels over at least two consecutive measurements taken at least 4 weeks apart. It is a reflection on how well the complement-mediated systemic thrombotic microangiopathy is being controlled by measuring platelet consumption and haemolysis.

Secondary endpoints:

Table 3: Secondary endpoints for studies C08-003 and C08-002

Study C08-003	Study C08-002
Progress in the rate of intervention for thrombotic microangiopathy (number of PE / FFP infusions and dialysis / patient / day) between the period prior to treatment with eculizumab and the period under treatment with eculizumab	
Progress in platelet count between the first dose of eculizumab and the end of the study (26 weeks)	Absence of signs of systemic thrombotic microangiopathy (as defined above) between the first dose of eculizumab and the end of the study (26 weeks)
Progress in score on EQ-5Dimensions[2] questionnaire	
Renal function: - Improvement in the stage of severity of renal impairment, - Progress in the estimated glomerular filtration rate (eGFR) (improvement by at least 15 ml/min/1.73 m^2) - Reduction in renal damage (proteinuria)	
Improvement in haemoglobin levels by at least 2 g/dl over the duration of the study	
Complete response (concerning systemic thrombotic microangiopathy)	

A complete response for systemic thrombotic microangiopathy corresponds to haematological normalisation criteria combined with an improvement in renal function (reduced plasma creatinine by at least 25%, sustained across two consecutive measurements taken at least 4 weeks apart).

Results:
The population analysed were those who received at least one dose of eculizumab.

[2] This questionnaire, which is non-disease specific, measures the benefit (preferences of patients) combined with general health and not the progress in quality of life linked to heath (overall health of patient).

Patient characteristics (see table 4):

Table 4: Characteristics of patients included in the two clinical studies

Characteristics	**Study C08-003 N = 20**	**Study C08-002 N = 17**
Median age, years (CI)	28 (13 – 63)	28 (17 – 68)
Gender - male, n (%)	8 (40)	5 (29)
Initial aHUS presentation, n (%)	5 (25)	7 (41)
Median duration of progress of current clinical complications, months (CI)	8.6 (1.2 – 45)	0.75 (0.23 – 3.70)
Median duration of progress since aHUS diagnosis, months (CI)	48 (0.66 – 286)	9.70 (0.26 – 236)
Mutation(s) and/or auto-antibodies identified, n (%)	14 (70)	13 (76)
Number of PE/FFP infusions in the 7 days prior to first dose of eculizumab, median (CI)	2 (1 – 3)	6 (0 – 7)
History of dialysis, n (%)	2 (10)	6 (35)
History of kidney transplant, n (%)	8 (40)	7 (41)
Stage 3-5 renal impairment, n (%)	18 (90)	17 (100)
Stage 4-5 renal impairment, n (%)	10 (50)	12 (70)
Initial platelet count, median ($x10^9$/l) (CI)	218 (105 – 421)	118 (62 – 161)
Initial LDH level, median (U/l) (CI)	200 (151 – 391)	269 (134 – 634)
Initial creatinine, median (µmol/l) (CI)	234 (106 – 893)	256 (124 – 787)

CI: 95% confidence interval

- Study C08-003

Patients had a mean age of 28 years; five adolescents were included. Patients were primarily women (60%).
Diagnosis of aHUS was known for these patients, with a median time since diagnosis of 48 months. These patients were having PE or chronic FFP infusions (for over 5 months for 75% of patients); the majority had a normal platelet count and LDH levels. The median duration of renal impairment (severe stage between 3 and 5 and eGFR < 60 ml/min/1.73 m^2) was 6 months for 90% of patients with renal impairment.

- Study C08-002

Patients had a mean age of 28 years; a single patient was under 18 years. These patients were primarily female (71%).
Diagnosis of aHUS was recent for these patients (median of 10 months). The frequency of PE or FFP infusions, persistence of thrombocytopenia, haemolysis (highlighted by increase in LDH levels) and the severity of renal impairment were signs of progressive systemic thrombotic microangiopathy. All patients had an altered renal function at inclusion (stages 3 to 5, eGFR < 60 ml/min/1.73 m^2). Six patients had had dialysis in the 56 days prior to the start of treatment, including one patient who stopped dialysis before being put on eculizumab. Thus, there were five patients on dialysis at the start of treatment.

Primary efficacy endpoints (see table 5):

- Study C08-003

Of the 20 patients included, 16 did not have signs of thrombotic microangiopathy after 26 weeks of treatment, which is 80% of patients (95% CI = [56; 94]).

Haematological normalisation at 26 weeks was achieved by 18 patients, which is 90% of patients included (95% CI = [68; 99]).

- Study C08-002

After 26 weeks, the platelet count had increased by 73 x 10^9 platelets/l (95% CI [40x10^9; 105x10^9]; p = 0.0001).

Haematological normalisation at 26 weeks was achieved by 14 out of 17 patients included, which is 82% of patients (95% CI = [57; 96]).

Table 5: Efficacy results from studies C08-003 and C08-002 at 26 weeks (primary efficacy endpoints)

Endpoints (26 weeks)	**C08-003 n = 20**	**C08-002 n = 17**
Absence of signs of TMA n (%) (95% CI)	16 (80) [56; 94]	15 (88) [64; 99]
Progress in platelet count compared with inclusion x10^9/l (95% CI)	5.28; p = 0.64	73 [40; 105]; p = 0.0001
Normalisation in platelet count n (%) (95% CI)	18 (90) [68; 99]	14 (82) [57; 96]
Intervention for TMA:		
- rate of daily intervention pre-eculizumab, median (min max)	0.23 [0.05; 1.09]	0.88 [0.04; 1.59]
- rate of daily intervention on eculizumab, median (min max), p vs. level pre-treatment	0 [0; 0]; p < 0.0001	0 [0; 0.31] p < 0.0001
Improvement ≥ 1 stage of CRI n (%) (95% CI)	7 (35) [15; 59]	10 (59) [33; 82]
Progress in eGFR compared with inclusion ml/min/1.73 m^2	+6; p < 0.0001	+31; p < 0.0001
Progress in eGFR compared with inclusion ≥15 ml/min/1.73 m^2, n (%) (95% CI)	1 (5) [0; 25]	8 (47) [23; 72]
Stable progress in Hgb > 20 g/l, n (%) (95% CI)	9 (45) (23-68)	11 (65) (38-86)
Haematological normalisation, n (%) (95% CI)	18 (90) (68-99)	13 (76) (50-93)
Complete response for TMA, n (%) (95% CI)	5 (25) (9-49)	11 (65) (38-68)

Secondary endpoints:

In the two studies, improvements were observed for all the endpoints investigated based on rate of intervention for thrombotic microangiopathy, renal function, haemoglobinaemia, haematological normalisation and complete responses (see table 6). These improvements appeared to be more significant in patients resistant to PE and FFP infusions.

Intermediate results from the follow-up studies suggest that efficacy is maintained in the long-term (median of 62 weeks for study C08-003 and 64 weeks for study C08-002, see table 6).

Table 6: Efficacy results for studies C08-003 and C08-002 during the follow-up period

Endpoints	C08-003, n = 20	C08-002, n = 17
	Median duration 62 weeks	Median duration 64 weeks
Absence of signs of TMA n (%) (95% CI)	17 (85)	15 (88) [64; 99]
Progress in platelet count compared with inclusion x10^9/l (95% CI)	17.4; p = 0.3508	90 [69; 111] (52 weeks); p<0.0001
Normalisation in platelet count n (%) (95% CI)	19 (95) [75; 100]	15 (88) [64; 99]
Intervention for TMA:		
- rate of daily intervention pre-eculizumab, median (min max)	0.23 [0.05; 1.09]	0.88 [0.04; 1.59]
- rate of daily intervention on eculizumab, median (min max), p vs. level pre-treatment	0 [0; 0]; p<0.0001	0 [0; 0.31] p<0.0001
Improvement ≥ 1 stage of CRI n (%) (95% CI)	9 (45) [23; 68]	11 (65) [38; 86]
Progress in eGFR compared with inclusion ml/min/1.73 m^2	+8.3; p<0.0001	+42.8; p=0.0041
Progress in eGFR compared with inclusion ≥15 ml/min/1.73 m^2, n (%) (95% CI)	3 (15) [3; 38]	9 (53) [28; 77]
Stable progress in Hgb > 20 g/l, n (%) (95% CI)	10 (50) (27-73)	13 (76) (50-93)
Haematological normalisation, n (%) (95% CI)	18 (90) (68-99)	15 (88) (64-99)
Complete response for TMA, n (%) (95% CI)	7 (35) (15-59)	13 (76) (50-93)

3.1.2. Supplementary data

Retrospective study C09-001r
This retrospective observational study included 30 patients with aHUS who were treated with eculizumab but not included in clinical trials.

Inclusion criteria:
- male or female of any age with an established aHUS diagnosis.
- patients received at least one dose of eculizumab for treatment of aHUS between 2007 and December 2009 but not within the context of a clinical trial.

Treatment:
The duration and doses of treatment varied according to the patient, the choice of dose being at the discretion of the treating physician, or where necessary after contact with the manufacturing laboratory, especially in paediatric cases where dose based on body weight was not able to be established after pharmacokinetic/pharmacodynamic modelling.
Therefore, patients could receive a single dose or chronic administration of eculizumab at doses of 300, 600, 900 or 1200 mg.

Efficacy endpoints:
- Reduction in systemic thrombotic microangiopathy:
  - Normalisation of platelet count (≥ 150 10^9/l across at least two consecutive measurements taken at least four weeks apart),
  - Progress in the rate of intervention for thrombotic microangiopathy (number of PE/FFP infusions and dialyses per day, per patient) between the pre-treatment and treatment period,
  - Absence of signs of thrombotic microangiopathy (for at least 12 weeks: no reduction in platelet count by more than 25% of the initial count, no PE/FFP infusions and no new patients on dialysis).
- Progress in haemoglobin levels (≥ 2 g/dl across at least two consecutive measurements taken at least 4 weeks apart).

- Progress and normalisation of LDH levels (≤ ULN across at least two consecutive measurements taken at least 4 weeks apart),
- Renal function (progress in the stage of severity in renal impairment, eGFR, creatinine).
- Haematological normalisation: normalisation in platelet count and LDH levels (for patients with initially abnormal counts) and complete response in terms of thrombotic microangiopathy (haematological normalisation combined with an improvement in renal function, defined as a reduction by at least 25% in serum creatinine).

Results for the total study population:

The majority of patients included were children and adolescents (19/30 or 63%): 5 were under 2 years (17%), 10 between 2 and 11 years (33%), 4 between 12 and 18 years and 11 were over 18 years.
The median duration of disease progression since diagnosis was 10.9 months. Patients had been treated with eight PE/FFP infusions (median) in the 28 days prior to the first dose of eculizumab.
A mutation of a complement regulator factor or auto-antibodies was identified for 14 patients (47%).
Among the 30 patients, 20 had aHUS that was resistant to PE (worsening in HUS ≤ 2 months) and 8 had chronic aHUS (worsening in HUS > 2 months).
Thirteen patients had stage 4-5 renal impairment, 11 had a previous history of dialysis and 11 had previously had a kidney transplant.
On inclusion, the median platelet count was $159x10^9$/l and the median LDH level was 453 U/l.

After treatment, improvements were observed in particular in terms of (see table 6):
- normalisation in platelet count measured at 26 weeks: 25/30 patients (83%), with a count ≥ $150x10^9$/l), mean improvement in platelet count was $84x10^9$/l measured at 364 days;
- signs of thrombotic microangiopathy: 20 patients (67%) had no sign (measured at the end of the participation for patients);
- the median intervention rate for thrombotic microangiopathy per patient per day (measured at the end of the participation for patients): reduction from 0.34 to 0.00 (2 patients were undergoing dialysis and 9 patients PE).

Haematological normalisation (measured at 26 weeks) was achieved by 10 patients (33%), an improvement in estimated glomerular filtration rate by at least 15 ml/min/1.73 m^2 (measured at the end of the patient participation period) by 11 patients (37%) and an increase in haemoglobinaemia by at least 2 g/dl (measured at the end of the patient participation period) by 13 patients (43%).
A complete response was achieved by 10 patients (33%).

Table 7: efficacy results for study C09-001r

Endpoints	**Patients treated with eculizumab** n = 30
Normalisation in platelet count (≥ 150×10^9/l), % (95% CI)	83 [65; 94]
Absence of signs of systemic TMA over 12 weeks (according to endpoint definition), % (95% CI)	67 [47; 83]
Haematological normalisation, %	33
Median intervention rate for TMA (number of PE/FFP infusions/dialysis /patient/day) (95% CI)	Pre-treatment: 0.34 [0.00; 2.38] Under treatment: 0.00 [0.00; 0.41] ($p < 0.0001$)
Improvement in estimated glomerular filtration rate (eGFR) by at least 15 ml/min/1.73 m^2, % (95% CI)	37 [20; 56]
Improvement in haemoglobin by at least 2 g/dl, % (95% CI)	43 [25; 63]
Compete response (for TMA), %	33

Results for the paediatric population (a posteriori analysis carried out by EMA):

Half the population included was patients aged under 12 years.
A mutation of a complement regulator factor or auto-antibodies was identified for 7 of the 15 patients.
Platelet count dropped for 7 patients and LDH increased for 10 patients. Renal impairment was severe (stage 4-5) for 3 patients.

As with the total study population, improvements were observed in patients aged under 12 years for all the parameters investigated:

- the median intervention rate for thrombotic microangiopathy was reduced from 0.45 per patient and per day (during the 28 days prior to the first dose of eculizumab) to 0 in 15 patients aged under 12 years;
- 11 patients did not have any signs of thrombotic microangiopathy over the 12 week treatment period;
- 14 patients achieved or maintained a normal platelet count, specifically 6 of the 7 patients who had thrombocytopenia at the start of treatment;
- Renal function improved, with an increase in eGFR of at least 15 ml/min/1.73 m^2 in 8 patients. Dialysis was not needed by these patients. Of the 6 patients who received dialysis treatment in the 28 days prior to starting treatment, 1 stopped dialysis before entry in the study, and, of the 5 who remained, 4 stopped dialysis on a permanent basis during the study;
- a complete response was achieved by 7 children and biological parameters were stabilised in 5 patients.

Clinical cases reported in the literature

Numerous cases of patients with aHUS and treated with eculizumab have been reported in the literature since 2009, with 20 cases in total being described in 15 published articles and 5 different abstracts.
Of the cases described, there were eight children under 12 years, four adolescents under 18 years and eight adults.
There were nine cases of aHUS clinical complications following a kidney transplant and two cases of prophylactic treatment with eculizumab started pre- and/or post-kidney transplant without any signs of the disease.

Details of these cases are in the tables in the Appendix.

For all cases, a stable improvement over time was observed for the haematological endpoints, the signs of thrombotic microangiopathy and renal function, with the exception of two patients. It should be noted, however, that these patients only received a single dose of eculizumab. After a phase of improvement in their clinical state, signs of the disease reappeared, combined with chronic renal impairment.

3.2. Adverse effects/safety

3.2.1. Results from the studies

- Study C08-003A/B

The mean duration of exposure to eculizumab was 40 weeks. All patients were exposed for at least 26 weeks.

Adverse events linked to treatment were reported in 6/20 patients. Headaches (n = 2), leucopenia (n = 2) and lymphopenia (n = 2) were the most commonly reported effects. These were mild to moderate in severity.

Serious adverse effects included peritonitis (n = 1) and venous disorders (n = 1).

No meningococcal infections were reported.

- Study C08-002A/B

The mean duration of exposure to eculizumab was 37.7 weeks. Fifteen of the 17 patients were exposed for at least 26 weeks.

Adverse events linked to treatment were reported in 10 patients.
The most common were: leucopenia (n = 2), nausea (n = 2), vomiting (n = 2) and hypertension (n = 2). The severity of these effects was considered to be mild.

No meningococcal infection was observed.

One serious case of hypertension was reported.

No deaths occurred during the trial.

- Study C09-001r

At least one adverse event was reported by 22 of the 30 patients (73%), the most common including fever (n = 9), diarrhoea (n = 8), vomiting (n = 7), cough (n = 7) and infection of the upper respiratory tract (n = 6).

Of the seven infections of the 14 observed in six patients, six were considered to be possibly linked to treatment with eculizumab. The majority of infections were considered to be severe. All patients recovered fully, except for one who died following pulmonary aspergillosis.
One meningococcal infection occurred in one patient; however this was outside the analysis period. The patient recovered fully and continued to take treatment with eculizumab.

Thrombotic events occurred in two patients being treated. The first patient presented with a non-occlusive thrombosis of the right jugular vein at the central catheter. The second patient, who had a previous history of diffuse vascular disease, presented with three thromboses, which were complications of vascular surgery linked to this underlying condition.

Two deaths were reported, however they were not judged as being linked to treatment.

3.2.2. Summary of product characteristics

Adverse effects classified as very common (≥ 10%) were leucopenia and headaches.

Adverse effects classified as common (≥ 1/100, <1/10) were: infections, thrombocytopenia, haemolysis, anaphylactic reaction, dizziness, dysgeusia, paraesthesia, accelerated hypertension, cough, nasal congestion, pharyngolaryngeal pain, throat irritation, gastrointestinal disorders, alopecia, dry skin, pruritus, rash, arthralgia, lower back pain, myalgia, neck pain, pain in the extremities, dysuria, spontaneous penile erection, chest discomfort, chills, fatigue, asthenia, infusion related reaction, oedema, fever, and positive Coombs test.

Cases of thrombotic microangiopathy were reported when administration of SOLIRIS was missed or delayed.

3.2.3. Pharmacovigilance data

Pharmacovigilance data for eculizumab concerns its use as a treatment for paroxysmal nocturnal haemoglobinuria. This data covers the period from April 2010 to April 2011.
It is estimated that a total of 1666 patients were treated during this period with 1363 adverse events being reported, including 370 that were serious.
Seventy-one patients died, with deaths being most commonly linked to an underlying condition or co-morbidity. Eight cases of meningococcal infection were reported, including two which led to the death of the patient. Frequency of infection was estimated at 0.46 for 100 patient-years.
Low levels of auto-antibodies were detected in 2% of patients being treated with eculizumab, not impacting on pharmacodynamic parameters or clinical results. To date, there have been no patients who developed neutralising antibodies.

3.3. Conclusion

The evaluation of eculizumab for atypical haemolytic uremic syndrome (HUS) is based on two non-comparative phase II studies:

- one on 20 adults/adolescents with aHUS sensitive to plasmatherapy, with a stable platelet count and chronic renal impairment, and treated in the long-term with plasma exchange (PE) or fresh frozen plasma infusions (FFPI),
- the other on 17 adults/adolescents with aHUS resistant to plasmatherapy with progressive systemic thrombotic microangiopathy (lowered platelet count and elevated LDH), and impairment of vital organs (renal impairment).

Patients received an intravenous injection of 900 mg of eculizumab per week over 4 weeks (initial phase) following the last administration of FFP or the last PE, then a dose of 1200 mg in the 5^{th} week and every 14 days thereafter, up to 26 weeks (maintenance phase). After the 26th week, treatment with eculizumab could be continued within the scope of follow-up studies.

After 26 weeks, an improvement was observed for the two primary efficacy endpoints:

- for the 20 patients with aHUS sensitive to plasmatherapy, 16 (80%; 95% CI = [56; 94]) did not have signs of thrombotic microangiopathy and 18 (90%; 95% CI = [68; 99]) achieved haematological normalisation.
- In the 17 patients with aHUS resistant to plasmatherapy, platelet count increased by $73x10^9$ platelets/l (95% CI [40×10^9; 105×10^9]; p = 0.0001) and haematological normalisation was achieved by 14 patients (82%; 95% CI = [57; 96]).

Despite the apparently convincing results, regrettably the methodology for the demonstration of the efficacy of eculizumab is of poor quality, there is an absence of morbidity data (quality of life, visceral impact, particularly renal), an absence of characterisation of efficacy based on the genetic aetiology or not of aHUS and an absence of an investigation into the follow-up and discontinuation of treatment criteria, especially in cases of non-genetic forms.

Eculizumab has also been evaluated in a retrospective observational study on 30 patients with aHUS (20 resistant to PE and 8 chronic; median platelet count 159x10^9/l) treated between 2007 and December 2009 with eculizumab at variable doses and treatment durations. Improvements were observed in terms of:

- platelet count: at 26 weeks normalisation (≥ 150x10^9/l in 25 patients (83%); at 52 weeks mean improvement 84x10^9/l);
- signs of thrombotic microangiopathy: no signs in 20 patients (67%);
- intervention rate for thrombotic microangiopathy: decrease in median rate per patient per day from 0.34 to 0.00 (2 patients received dialysis treatment and 9 patients had PE);
- haematological effects: normalisation in 10 patients (33%);
- estimated glomerular filtration rate: increase by at least 15 ml/min/1.73 m^2 in 11 patients (37%);
- haemoglobinaemia: increase by at least 2 g/dl: 13 patients (43%);
- complete response in 10 patients (33%).

Twenty cases of aHUS treated with eculizumab have been reported in the literature with a persistent improvement over time in haematological endpoints, signs of thrombotic microangiopathy and renal function, except for two patients who only received a single dose of eculizumab.

In these studies, the most common adverse events linked to treatment observed were: leucopenia, headaches, nausea, vomiting, hypertension, fever, infections including pulmonary aspergillosis (1 case) and meningococcal infection (1 case).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Atypical HUS is a very rare, genetic disorder involving an absence of regulation of the alternative complement pathway. It is a very severe disease that can lead to serious complications to various organs through complement-mediated thrombotic microangiopathy, in particular to the kidneys, with progress towards terminal renal failure and resulting in a short-term life-threatening prognosis.

This proprietary medicinal product is intended as curative treatment.

Public health benefit:

In terms of public health, while atypical haemolytic uremic syndrome is a serious life-threatening condition, the burden on public health of this disease is considered to be low because it is rare (rare disease).

Improvement in the management of orphan diseases, including tailoring medication to the specific needs of the patient, in particular by facilitating access to specific medicinal products, is a public health need that is an established priority (first topic of the second Rare Disease Plan 2011-2014).

In view of the available data, based on a restricted number of patients, this proprietary medicinal product is expected to have a moderate impact on morbidity (asthenia, renal damage) compared with available treatments (plasma exchanges and fresh frozen plasma infusions). There is insufficient long-term data to determine the impact in terms of multi-visceral complications and mortality. The impact on quality of life is difficult to assess, based on data presented from the generic questionnaire (EQ-5D) that measures the benefit (preferences of patients) combined with general health and not the progress in quality of life related to heath (overall state of patient).

Furthermore, SOLIRIS should enable there to be fewer plasma exchanges, fresh frozen plasma infusions and dialysis treatments. A positive impact on the healthcare system should therefore be expected.

However, given the very small number of patients concerned, the impact of SOLIRIS on the population can only be small.

Therefore, SOLIRIS is expected to meet an identified public health need.

Consequently, in the current state of knowledge, it is expected to have a public health benefit. This benefit is slight.

The efficacy/adverse effects ratio is high.

This medicinal product is a first-line therapy.

There are no other alternative medicinal products.

The actual benefit of SOLIRIS 300 mg, concentrate for solution for infusion, is substantial in this indication.

4.2. Improvement in actual benefit (IAB)

SOLIRIS 300 mg, an orphan medicine, provides an important improvement in actual benefit (IAB II) compared to standard treatment for patients with aHUS.

4.3. Therapeutic use

Haemolytic uremic syndrome (HUS) or systemic thrombotic microangiopathy combines haemolytic anaemia with schistocytes, thrombocytopenia and visceral damage, especially to the kidneys and central nervous system, and more rarely to the digestive tract and the heart. Atypical HUS represents 10% of all HUS cases.
Current treatment for patients with aHUS is plasma exchange and fresh frozen plasma infusions. However these treatments, which are symptomatic and do not have an effect on the disruption of the complement, are not validated and are associated with serious complications. Fresh frozen plasma transfusions can lead to volume overload, hypertension, heart failure and hyperproteinaemia. Plasma exchanges can lead to hypotension or hypocalcaemia.
Haemodialysis or a kidney transplant may be necessary in cases of terminal renal failure. However, symptoms of thrombotic microangiopathy remain present, and the risk of damage and rejection of the transplanted organ are significant.

Eculizumab, a class IgG2 monoclonal humanised antibody, targeting the C5 terminal fraction, is the first medicinal product with an effect on the regulation of the alternative complement pathway. It is a first-line treatment. Supplementary clinical data is required so that the population who could benefit the most from SOLIRIS can be better defined, based on the aetiology of the disease, as well as the criteria for follow-up, discontinuation or restarting of treatment. The risk of infection (in particular, *Neisseria meningitidis* meningitis) is to be taken into account during treatment monitoring.

4.4. Target population

The target population for SOLIRIS is defined as only children and adults with aHUS. SOLIRIS is not indicated in cases of HUS resulting from infection.

Atypical HUS is a very rare disease. According to Orphanet data,[3] the prevalence of aHUS in Europe is 1/100,000, which when relating this value to the French population (INED 2011 data), is a target population of 650 patients.

[3]Orphanet documents: Prevalence of rare diseases: bibliographic data, May 2012.

The incidence of genetic forms of aHUS is 10 to 20 new cases per year in France, and non-genetic forms are 2 to 3 times more common, i.e. a total of 20 to 60 new cases of aHUS per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

Request for a study:
The Transparency Committee would like to gather supplementary data on the management of patients with aHUS. The use of existing registers (especially the register for thrombotic microangiopathy) is advocated. In particular, data on the criteria for stopping and potential restarting of SOLIRIS are expected. The use of SOLIRIS outside the indication of the Marketing Authorisation should also be characterised and quantified.
The Committee is also waiting for the definitive results from follow-up studies beyond 26 weeks of treatment from studies C08-002 and C08-003.

Packaging: Appropriate for the prescription conditions.

APPENDIX: Summary of cases reported in the literature

References	Age / Sex	Medical history	Pre-eculizumab period	Eculizumab dose	Efficacy	Adverse Effects
Gruppo RA et al. 2009[1]	18 months M	Atypical HUS diagnosed at 8 days 3 series of clinical complications (3, 9, 11 and months): stabilisation with PE/FFPI	4th clinical manifestation: no response despite 32 days of PE/FFPI	Initiated on Day 35: 300 mg / week over weeks Maintenance: 600 mg every 2 weeks	Haematological and renal function improvement from Day 2, response after 10 days, maintained at 4 months Day 20: normalisation of platelets and LDH, creatinine approaching normal	Not reported
Mache CJ et al. 2009[2]	17 years M	Initial aHUS presentation	Persistent TMA despite PE/FFPI, deterioration in renal function	Single dose of 600 mg	At Day 5: normalisation of platelet count and haptoglobin Improvement in renal function At 2 weeks: TMA recovery 3 doses eculizumab over 6 days: haptoglobin normalisation but TRF with need for haemodialysis New complication: anuria	Not reported
Nürnberger J et al. 2009[3]	37 years F	Atypical HUS diagnosed at 25 years 2 kidney transplants (30 and 37 years) with clinical complications	Clinical complication with 2nd transplant: deterioration in renal function despite 4 PE/FFPI	Single dose of 600 mg	Haemolysis eliminated, recovery of renal function Stable at 8 months	Not reported
Al-Akash SI et al. 2010[4]	15 years M	TRF with aHUS at 16 months 2 kidney transplants (2 ½ years and 8 years) with clinical complications	3rd transplant: prophylaxis with PE/FFP infusions pre/post-transplant At 2 months: A/H1N1 infection with TMA at biopsy PE/FFPI over 11 days Eculizumab initiated after 9th PE/FFPI	900 mg then 900 mg on Day 2 (post last PE/FFPI) Total of 4 induction doses of 900 mg over 4 weeks Maintenance: 1200 mg every 2 weeks	After induction: creatinine at 1.6 mg/dl Biopsy: improvement in TMA at 6 months, absence of TMA at 12 months Stable at 13 months with C3 very low and creatinine 1.2-1.4 mg/dl Continued normal education and physical activities, including competitive sport	Not reported

F: female, ARI: acute renal impairment, TRF: terminal renal failure, M: male, TMA: thrombotic microangiopathy, PE/FFPI: plasma exchange/fresh frozen plasma infusion, atypical HUS: atypical haemolytic uremic syndrome, * abstract

References	Age / Sex	Medical history	Pre-eculizumab period	Eculizumab dose	Efficacy	Adverse Effects
Châtelet V et al 2010[5]	42 years F	TRF at 30 years 2 kidney transplants (34 and 37 years) with clinical complications	Worsening of aHUS at 3 years post-2nd transplant: stabilisation on PE/FFPI but diarrhoea, fatigue Decision to stop PE/FFP infusion: eculizumab	Initiation at Day 4 post-last PE/FFPI: 900 mg/week over 4 weeks Maintenance: 1200 mg every 2 weeks	17 months of treatment without PE/FFPI Lowering in schistocytes, normalisation of haptoglobin, stabilisation of creatinine, no diarrhoea Interval between administration of 2 doses of eculizumab: temporary return of TMA, eliminated after new dose Significant improvement in quality of life and fatigue	Not reported
Davin JC et al. 2010[6]	17 years F	Atypical HUS diagnosed at 3 years 2 kidney transplants (5 and 12 years) with clinical complications Neurological complications	3rd transplant with prophylaxis with PE/FFPI: neurological complications, TMA and elevated creatinine Development of allergic reaction to plasma requiring adrenalin: stop PE/FFPI (cerebrovascular risk)	Initiation after last PE/FFPI: 900 mg/week over 4 weeks Maintenance: 1200 mg every 2 weeks	At 6 months: creatinine stable 1.36 mg/dl, no significant change in haemoglobin, haptoglobin or LDH, platelet count normal	No adverse events
Köse O et al. 2010[7]	18 years F	Initial aHUS presentation Possible trigger linked to oral contraception started 2 months previously	No stabilisation with PE/FFPI (18 sessions)	Single dose of 600 mg	Improvement in haemolysis and renal function in 1 week, normalisation of platelet count, dialysis stopped At 2 moths: complication and TRF	Not reported
Lapeyraque AL et al. 2010[8]	7 years F	Diagnosis of atypical HUS at 7 months 11 series of clinical complications: chronic glomerular lesions, active disease (elevated creatinine)	6 years: severe clinical complication after episode of diarrhoea, no stabilisation with PE/FFPI	Initiation at Day 10 (stop PE/FFPI): 600 mg/week over 3 weeks Maintenance: 600 mg every 2 weeks	At 1 week: elimination of AHT, increase in platelet count, normalisation of haptoglobin, return of renal function to initial level Stable at 12 months, no complication, despite viral infections, creatinine normal	Not reported

F: female, ARI: acute renal impairment, TRF: terminal renal failure, M: male, TMA: thrombotic microangiopathy, PE/FFPI: plasma exchange/fresh frozen plasma infusion, atypical HUS: atypical haemolytic uremic syndrome, * abstract

References	Age / Sex	Medical history	Pre-eculizumab period	Eculizumab dose	Efficacy	Adverse Effects
Larrea CF et al. 2010[9]	22 years F	Atypical HUS diagnosed at 20 years (postpartum) No stabilisation with PE/FFPI: TRF Kidney transplant at 22 years	Clinical complication Day 12 post-transplant: no stabilisation with PE/FFPI	Single dose of 600 mg	At Day 4: normalisation of platelet count and renal function Stable at 7 months without treatment	Not reported
Prescott HC et al. 2010[10]	47 years F	Initial aHUS presentation TMA and ARI	On PE/FFPI: stabilisation of creatinine, improvement in LDH and platelets Deterioration at 2 weeks despite PE/FFPI: lowered platelet and deterioration in renal function	Initiation: 900 mg/week over 4 weeks Maintenance: 1200 mg every 2 weeks	Continued improvement in renal function	Well tolerated, no infections or other complications
Zimmerhackl LB et al. 2010[11]	9 years M	Atypical HUS diagnosed at 4 years On dialysis for 6 years	Septicaemia at catheter: deterioration in renal function Kidney transplant: normalisation post-transplant with PE/FFPI up to Day 9 then eculizumab as prophylaxis	1st dose Day 10 post-transplant: 600 mg Maintenance: 600 mg every 2 weeks	At 1 year post-transplant: no sign of disease activity (platelets and haptoglobin normal), normal renal function	Not reported
Chandran S et al. 2011[12]*	34 years F	Initial aHUS presentation Post-kidney and pancreas transplant (TRF secondary to type I diabetes)	Day 2 post-transplant: deterioration in renal function, TMA No stabilisation on PE/FFPI	1st dose 1200 mg 2nd dose 900 mg at 1 week	Improvement in platelet count, LDH and renal function from Day 2 Stable at 4 months with LDH, platelets and haemoglobin normal	Not reported

F: female, ARI: acute renal impairment, TRF: terminal renal failure, M: male, TMA: thrombotic microangiopathy, PE/FFPI: plasma exchange/fresh frozen plasma infusion, atypical HUS: atypical haemolytic uremic syndrome, * abstract

References	Age / Sex	Medical history	Pre-eculizumab period	Eculizumab dose	Efficacy	Adverse Effects
Nester C et al. 2011[13]*	12 years F	Atypical HUS diagnosed at 8 years Kidney transplant at 8 years with clinical complication	Complications at 25 months post-transplant: TMA, ARI with AHT Partial Stabilisation with PE/PI without recovery of renal function Decision kidney transplant combined with eculizumab	1 week before transplant: PE/FFPI + 900 mg eculizumab 1 day before transplant: PE/FFPI Day of surgery: 900 mg eculizumab 3rd-4th doses at 1 and 2 weeks post-transplant: 900 mg Maintenance: 900 mg every 2 weeks	Creatinine: reduced to 133 µmol/l at Day 7, no TMA C3 normalised in 2 weeks At 4 months: creatinine continues to fall (80 µmol/l), no haemolysis, BP normal, return to normal life	Not reported
Ohanian M et al. 2011[14]*	50 years F	Initial aHUS presentation	TMA confirmed after total colectomy Neurological and respiratory decline, deterioration in renal function	Initiation: 900 mg/week over 4 weeks Maintenance: 1200 mg every 2 weeks From 7th dose: 600 mg every week due to nausea	Normalisation LDH, haptoglobin after 6th dose Continued improvement in renal function with dialysis stopped after 4th dose Total recovery of neurological function	Nausea: eliminated after changes to therapeutic regimen
Weitz M et al. 2011[15]*	7 years M	Atypical HUS diagnosed at 6 months	Difficulty performing haemodialysis: emergency kidney transplant Prophylactic treatment with eculizumab	Initiation: 600 mg in 1st week, 300 mg the 2nd week 600 mg immediately before and after transplant Maintenance: 300 mg every 2 weeks (with several doses at 600 mg) Transplant after 3 weeks	Stable at 7 months with normal renal function and absence of haemolysis Absence of haemolysis despite incomplete inhibition of complement activity	Absence of complications
Fremont O et al. 2009[16]*	4 years M	Initial aHUS presentation	Following respiratory infection Partial stabilisation with PE/FFPI	Initiation: 300 mg/week over 4 weeks Maintenance: 600 mg every 2 weeks	Normalisation of LDH, platelets and haemoglobin in 2 weeks Stable at 10 weeks	Not reported

F: female, ARI: acute renal impairment, TRF: terminal renal failure, M: male, TMA: thrombotic microangiopathy, PE/FFPI: plasma exchange/fresh frozen plasma infusion, atypical HUS: atypical haemolytic uremic syndrome, * abstract

References	Age / Sex	Medical history	Pre-eculizumab period	Eculizumab dose	Efficacy	Adverse Effects
Legault DJ et al. 2009[17]*	34 years F	Atypical HUS diagnosis Kidney transplant at 34 years	1 month post-transplant: ARI, TMA Stabilisation with PE/FFPI 5 months post-transplant: clinical complication, no stabilisation with PE/FFPI	Initiation: 900 mg/week over 4 weeks Maintenance: 1200 mg/week every 2 weeks	At 4 weeks: stabilisation of creatinine At 7 weeks: absence of TMA at biopsy Stable at 6 months, improvement in creatinine, platelet count and haptoglobin normal	Not reported
Ardissino et al. 2010[18]*	6 years M	Initial aHUS presentation	Kidney transplant with PE/FFPI as pre/post-transplant prophylaxis Complication post-transplant at 2 months: no stabilisation with PE/FFPI	1st dose of 600 mg 2 additional doses at 1 and 2 weeks	Response obtained: decrease in creatinine and LDH	Not reported
Häffner K et al. 2010[19]*	4 years M	Atypical HUS diagnosed at 14 months 7 series of clinical complications in 3 years	Over time: absence of stabilisation with PE/FFPI	Initiation: 600 mg then 300 mg at 1 week Maintenance: 300 mg every 2 weeks	Fast response: reduction in creatinine, reduction in proteinuria and improvement in AHT with no signs of TMA	Not reported
Tschumi S et al. 2010[20]*	9 years F	Initial aHUS presentation	Clinical complications if PE/FFPI delayed	600 mg every 2 weeks	At 9 months: absence of TMA, stable renal function, quality of life improved	Not reported

F: female, ARI: acute renal impairment, TRF: terminal renal failure, M: male, TMA: thrombotic microangiopathy, PE/FFPI: plasma exchange/fresh frozen plasma infusion, atypical HUS: atypical haemolytic uremic syndrome, * abstract

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