



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

27 January 2010

TEGELINE 50 mg/ml, powder and solvent for solution for infusion

Vial containing 0.5 g of powder and vial containing 10 ml of solvent plus transfer device and needles (CIP: 559 895-3)

Vial containing 2.5 g of powder and vial containing 50 ml of solvent plus transfer device and needles (CIP: 559 897-6)

Vial containing 5 g of powder and vial containing 100 ml of solvent plus transfer device and needles (CIP: 559 898-2)

Vial containing 10 g of powder and vial containing 200 ml of solvent plus transfer device and needles (CIP: 559 899-9)

Applicant: LFB-BIOMEDICAMENTS

“Normal human immunoglobulin”

ATC code: J06BA02

List I

Medicine for hospital prescription only. Prescription by doctors practising in a blood transfusion establishment who are authorised to dispense medicines to patients being treated there is also authorised.

Date of Marketing Authorisation: 2 September 1996

Amendment of Marketing Authorisation: 24 February 2009 (extension of the indication to chronic inflammatory demyelinating polyradiculoneuropathy)

Reason for the request: Inclusion on the list of medicines approved for hospital use in the extension of the indication to chronic inflammatory demyelinating polyradiculoneuropathy.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

“Normal human immunoglobulin”

1.2. Indication

- “Replacement therapy:
 - primary immunodeficiencies with hypogammaglobulinaemia or functional humoral immunodeficiency,
 - recurring bacterial infections in children infected with HIV,
 - secondary humoral immunodeficiencies, in particular:
 - chronic lymphoid leukaemia or myeloma with hypogammaglobulinaemia associated with recurrent infections,
 - haematopoietic stem cell transplant with hypogammaglobulinaemia associated with an infection.
- Immunomodulation:
 - idiopathic thrombocytopenic purpura (ITP) in adults and children at high risk of bleeding or prior to undergoing a medical or surgical procedure to correct the platelet count,
 - Birdshot retinochoroiditis,
 - Guillain-Barré syndrome in adults,
 - multifocal motor neuropathy (MMN),
 - **chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).**
- Kawasaki disease.”

1.3. Dosage

“The dosage and interval between doses depends on the intended purpose of treatment (replacement or immunomodulation) and the half-life of the intravenously-administered normal human immunoglobulin (IVIG) in vivo in patients with immunodeficiency. The following dosages are given as a guideline.”

“Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP):

The dosage of 2 g/kg administered over 5 days and repeated every 4 weeks may be maintained for a maximum of 4 months, depending on the response to treatment.

Absence of response must be evaluated at each cycle and if there is no response after 3 months, discontinuation of treatment must be considered.”

For the other indications, see the SPC.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

J	Antiinfectives for systemic use
J06	Immune sera and immunoglobulins
J06B	Immunoglobulins
J06BA	Immunoglobulins, normal human
J06BA02	Immunoglobulins, normal human, for intravascular administration

2.2. Medicines in the same therapeutic category

2.2.1. Strictly comparable medicines

TEGELINE is the only “normal human immunoglobulin” indicated in the treatment of chronic inflammatory demyelinating polyradiculoneuropathy.

2.2.2. Not strictly comparable medicines

Not applicable

2.3. Medicines with a similar therapeutic aim

CORTANCYL (prednisone) and SOLUPRED (prednisolone) have a closely-related indication, in the treatment of chronic idiopathic demyelinating polyradiculoneuropathy.

<h2>3 ANALYSIS OF AVAILABLE DATA</h2>
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The company's application is based on a retrospective clinical study (LFB 43-64-404) and on literature data.

3.1. Efficacy

3.1.1. Retrospective clinical study (LFB 43-64-404)

This is a retrospective, non-comparative, multicentre, French study in 26 CIDP patients naïve to IV immunoglobulin (IVIG) treatment, the objective of which was to study the efficacy and safety of TEGELINE in this indication.

This study was carried out between 1 January 1995 (first cycle of IVIG) and 31 December 2005 (last cycle of IVIG).

Inclusion criteria:

- patient over 18 years of age at start of first cycle of IVIG,
- patient diagnosed with CIDP,
 - disability of ≥ 1 on the Rankin scale (see Table 1),
 - electrophysiological or histological signs of primary demyelination,
 - stable or worsening clinical state (no spontaneous improvement):
 - characterised by a globally symmetric motor or sensorimotor deficit affecting more than one limb, diminished or abolished tendon reflexes, progressive or relapsing-remitting in course, resulting in the presence of neuropathy for more than 2 months.
- disease present for more than 6 months,
- patient not treated with a normal human immunoglobulin prior to the first cycle of IVIG (naïve patient),
- patient had received his/her first cycle of IVIG between 1 January 1995 and 31 December 2004.

Non inclusion criteria:

- Severe axonal electrophysiological disorders affecting the upper limbs only, pure motor syndrome meeting the diagnostic criteria of motor neuropathy with persistent conduction blocks, patient improves spontaneously.

- Associated systemic illness that could be the cause of the neuropathy (cancer, systemic lupus erythematosus, diabetes, paraproteinaemia and paraproteinuria if results obtained within the past 6 months, HIV infection).
- Patient who has received systemic corticoids, IVIG, plasma exchange, or any immunosuppressant in the 6 months prior to inclusion, with the exception of corticoids given at a constant dose for at least 3 months prior to inclusion or immunosuppressants begun at the start of the first cycle of IVIG or given at a constant dose for at least 6 months prior to inclusion.

Primary endpoint: Responder rate after 4 months of treatment (in percent). A patient was defined as a responder if there was a reduction of at least 1 point in the Rankin score in relation to the last recorded score prior to treatment with IVIG.

The IVIG responder rate was compared with that of patients treated with placebo estimated on the basis of data taken from the meta-analysis by van Schaik¹.

In the case of patients for whom the Rankin score was not evaluated at 4 months (n = 8), the last recorded score prior to 4 months was used as the missing 4-month score.

Table 1: Modified Rankin scale

Score	Description of disability
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability: Unable to attend to own bodily needs without assistance and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.

Among the secondary endpoints: Global evaluation by the investigator after 4 months.

Results:

A population of 26 patients (15 men and 11 women) with an average age of 51 years was included. The average time between first symptoms and diagnosis was 4.9 years. Disability was motor in 100% of patients, sensory in 80.8% and asymmetric in 26.9% of patients. The physiological criteria met the definition of the European INCAT² group in 100% of cases. The disease course was progressive in 69.2% of patients and relapsing-remitting in 30.8%. The mean duration of follow-up in the study was 9.4 months.

The Rankin score prior to treatment was 1 in 5 patients, 2 in 11 patients, 3 in 6 patients, 4 in 4 patients and 5 in 0 patients.

The mean administered IVIG dose was 1.8 ± 0.4 g/kg per cycle and the median IVIG dose was 2 g/kg. The mean number of cycles per patient was 3 (1-6).

At 4 months, the Rankin score was available for 25/26 patients and the evaluation of efficacy for 21/26 patients.

The analysis was carried out on 25 patients (1 patient was excluded on account of treatment with corticoids).

A reduction of at least one Rankin score point relative to baseline was achieved in 13/25 (52%) of patients treated with IVIG ($IC_{95\%} = [0.313; 0.722]$).

¹ van Schaik I.N. et al. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review. *Lancet Neurol* 2002; 1: 491-8

² European Inflammatory Neuropathy Cause and Treatment

In the meta-analysis of van Schaik (2002), the responder rate under placebo was 15%. The observed difference between the IVIG group in study LFB 43-64-404 (52%) and the historical placebo group (15%) is statistically significant ($p < 0.001$).

The investigators estimated that after 4 months, 18/21 patients had responded favourably to treatment: 14 experienced a neurological improvement, 3 remained stable and 1 was in remission. A neurological deterioration was observed in 3 patients in whom the initial response to treatment had been favourable. 4 patients could not be evaluated on account of missing data.

Note: In interpreting the results, account must be taken of the retrospective methodology of the study.

3.1.2. Literature data

The company has selected the four studies comparing the efficacy of IVIG with that of placebo that had been published in the literature at the time of conception of study LFB 43-64-404.

Hahn study (1996)³:

Placebo-controlled, double-blind, crossover study (2 periods of 4 weeks) in 30 patients with progressive or relapsing-remitting CIPD (AAN⁴ criteria). Patients were given an IVIG cycle of 0.4 g/kg for 5 consecutive days or placebo and were evaluated after 4 weeks. Patients achieving a reduction in NDS (neuropathy disability score) of ≥ 20 points were defined as responders.

In the 25 patients who completed the two crossover periods, a reduction in NDS⁵ relative to baseline of 24.4 ± 5.4 points was observed in the patients treated with IVIG.

In the analysis of the first crossover period (i.e. 15 patients in each group), the patients treated with IVIG showed a reduction in NDS relative to baseline of 35.6 ± 25 points. In the two analyses, the patients on placebo showed a mean increase in NDS of about 5 points and the observed differences versus IVIG were statistically significant ($p < 0.002$ and $p < 0.0001$).

Mendell study (2001)⁶:

Placebo-controlled, randomised, double-blind study of 33 patients with CIPD as defined by the AAN criteria. The patients were given two cycles of IVIG comprising administration of 1 g/kg on day 1, day 2 and day 21 ($n = 30$) or placebo ($n = 23$). The patients were evaluated on day 42.

At day 42, treatment with IVIG achieved an improvement in AMS⁷ relative to placebo (0.63 ± 0.16 vs. -0.10 ± 0.10 , $p = 0.006$), with an increase in AMS observed in 76% of patients treated with IVIG.

³ Hahn A.F et al. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy. A double-blind, placebo-controlled, cross-over study. *Brain* 1996; 119: 1067-1077

⁴ American Academy of Neurology

⁵ Neurological Disability Score: composite scale that evaluates cranial nerve impairment (6 items; right and left; 6 stages), motor deficits (19 items; right and left; 6 stages), motor deficits (19 items; right and left; 6 stages), tendon reflex deficits (5 items; right and left; 3 stages) and sensory deficits (8 items; right and left; 3 stages).

⁶ Mendell J.R. et al. and the Working Group on Peripheral Neuropathy. Randomised controlled trial of IVIG in untreated chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 2001; 56 February (2 of 2): 445-449

⁷ Average Muscle Score: Score measuring muscular strength. The AMS corresponds to the mean modified MRC score (see reference 9) covering 10 points, on 34 muscles.

Notes: The dosing regimen for IVIG treatment does not correspond to the one approved in the Marketing Authorisation.

Thompson (1996)⁸:

Placebo-controlled, double-blind, crossover study (2 periods of 4 weeks) of patients with progressive or relapsing-remitting CIPD (AAN criteria). Patients were given an IVIG cycle of 0.4 g/kg for 5 consecutive days or placebo and were evaluated after 4 weeks. A clinically relevant improvement was defined as improvement in at least 3 out of 6 criteria (various scales and tests evaluating mobility, including the MRC score⁹). The protocol allowed for the inclusion of 15 patients. However, the recruitment of patients was brought to a premature close after the 7th patient, following the publication of positive findings from the Hahn study (1996). A relevant clinical improvement was shown by 3 out of 7 patients treated with IVIG after 4 weeks and by 2 out of 7 patients after 6 months and 1 year.

Vermeulen (1993)¹⁰:

Placebo-controlled, randomised, double-blind study of 28 patients with CIPD as defined by the AAN criteria. Patients were given an IVIG cycle of 0.4 g/kg for 5 consecutive days or placebo and were evaluated on day 16 and day 21 after treatment.

An improvement of at least 1 point on the Rankin scale was shown by 4 out of 15 patients treated with IVIG and by 3 out of 13 on placebo.

Note: The hypothesis used as the basis for calculating the size of the study population did not allow for improvement in the placebo group.

3.1.3. Additional data not included in the dossier

Published placebo-controlled study

Hughes (2008)¹¹

Placebo-controlled, randomised, double-blind, crossover study of 117 patients with CIPD as defined by the criteria of the European INCAT group. In first period, patients were given a cycle of 2 g/kg IVIG over 2-4 days or placebo, followed by a cycle of 1 g/kg IVIG over 1-2 days or placebo every three weeks for 24 weeks. The patients who had not responded to treatment at the end of the first period received the other treatment during the second period. A responder was defined as an improvement of ≥ 1 point on the INCAT¹² disability scale or a stable score for 6 weeks or an improvement followed by a deterioration in score to the baseline value or to a lower value over a 6-week period or longer.

The responder rate after 24 weeks of treatment (primary endpoint) was 54% (32/59) in the group of patients treated with IVIG and 21% (12/58) in the placebo group (ITT analysis, $p = 0.0002$). The results were similar during the second period.

Note: The dosing regimen for IVIG treatment does not correspond to the one approved in the Marketing Authorisation.

⁸ Thompson N. et al. A novel trial design to study the effect of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol* 1996; 243: 280-285

⁹ Medical Research Council: disability scale based on a point score for muscular strength per muscle or muscle group from 0 (complete paralysis) to 5 (normal strength). Each limb is scored from 0 to 15. The total score goes from 0 (complete tetraplegia) to 60 (normal muscular strength).

¹⁰ Vermeulen M. et al. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study. *Journal of Neurology, Neurosurgery and Psychiatry*, 1993; 56: 36-39

¹¹ Hughes R.A.C. et al. Intravenous immunoglobulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study: a randomised placebo-controlled trial. *Lancet Neurol* 2008; 7: 136-44

¹² INCAT disability score: disability score from 0 to 12.

Published studies versus active comparators

Two randomised crossover studies of two periods of six weeks compared IVIG against plasma exchange in a single-blind study in 20 patients (Dyck, 1994¹³) and IVIG against oral prednisolone in a double-blind study in 32 patients (Hughes, 2001¹⁴). These studies found no difference between treatments.

Note: These studies contained significant methodological bias, in particular an IVIG dosing regimen that did not correspond to the Marketing Authorisation and absence of an ITT analysis (analysis on 17 patients) in the Dyck study and premature termination of the study (analysis on 24 patients), inadequate power (40 patients are needed to demonstrate a difference between treatments with a power of 80% and a significance level of 5%) and a nonstandard prednisolone dosing regimen (60 mg/day for 2 weeks, 40 mg/day for 1 week, 30 mg/day for 1 week, 20 mg/day for 1 week, 10 mg/day for 1 week and 10 mg/day for 1 week) in the Hughes study.

3.2. Adverse effects

In the retrospective study LFB 43-64-404, patients underwent follow-up for a mean period of 9.4 ± 3.8 months (median: 9.9 months) and received 3 ± 2 IVIG cycles on average. Thirty adverse events concerning 16/26 patients were reported, of which 29 were non-serious and 1 serious but not connected to the treatment.

Adverse events probably connected to the treatment were leukopenia (1 patient), thrombocytopenia (1 patient), nausea (1 patient), hyperthermia (1 patient), dizziness (1 patient), headache (8 patients), insomnia (1 patient) and laryngitis (1 patient).

Adverse events possibly connected to the treatment were a reaction at the injection site (1 patient), local skin reaction (1 patient), rash (1 patient) and paraesthesias (1 patient).

The most recent PSUR for TEGELINE covering the period from 1 February 2008 to 31 January 2009 did not appear to signal any new safety issues in respect of the SPC.

3.3. Conclusion

The efficacy of IVIG treatment in patients with chronic inflammatory polyradiculoneuropathy has been evaluated on the basis of a retrospective, non-comparative study carried out by the company and literature data from randomised, double-blind, placebo-controlled comparative studies.

In a retrospective study in 25 patients (of the 26 initially included), a clinically relevant improvement, defined as a mean reduction in Rankin score of at least one point, was observed in 13/25 (52%) patients treated with IVIG ($CI_{95\%} = [0.313; 0.722]$).

Of the five published randomised, double-blind, placebo-controlled studies, three showed a statistically significant difference in favour of IVIG in terms of reduction in muscular or sensory deficit:

- Hahn study (1996) in 25 patients: after 6 weeks of treatment, an improvement in NDS of approximately 30 points relative to placebo, a difference of 20 points being considered clinically relevant,

¹³ Dyck P.J. et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 1994 Dec; 36(6): 838-45

¹⁴ Hughes R.A.C. et al. INCAT Group. Randomised controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *An Neurol* 2001 Aug; 50(2): 195-201

- Mendell study (2001) in 33 patients: after 6 weeks of treatment, an AMS score of 0.63 ± 0.16 with IVIG versus -0.1 ± 0.1 with placebo,
- Hughes study (2008) in 117 patients: after 24 weeks of treatment, responder rate (response defined as an improvement of ≥ 1 point on the INCAT disability scale) of 54% (32/59) with IVIG and 21% (12/58) with placebo.

In a study (Thompson, 1996) brought to a premature close following the publication of positive findings from the Hahn study (1996), a clinical improvement (defined as improvement in at least 3 out of 6 criteria based on the various scales and tests evaluating mobility, including the MRC score) was observed in 3 out of 7 patients.

In one study (Vermeulen, 1993) in 28 patients, no statistically significant difference was observed between IVIG treatment and placebo.

Based on these data, the effect observed with IVIG compared with placebo appears substantial, though the level of proof for the demonstration of this efficacy is low (retrospective study with a historical placebo control, dosage does not always correspond to the Marketing Authorisation in the published studies, premature termination of the Thompson study, low study populations, Vermeulen study negative).

Two studies have compared IVIG with an active therapy, one with plasma exchange (Dyck, 1994), the other with oral corticoids (Hughes, 2001). These studies did not reveal any difference between treatments.

The main adverse effects observed with IVIG are headache and local reactions at the injection site.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare, acquired inflammatory neuropathy of autoimmune aetiology that affects the peripheral nerves and responds favourably to immunomodulatory therapy. It is a serious disease that develops into a severe disability and can shorten life expectancy in the event of complications: quadriplegia, respiratory insufficiency and swallowing difficulties are responsible for 3 to 11% of deaths in patients with this disease.

This product is intended as curative therapy.

Public health benefit:

CIDP is a serious disease that represents a low public health burden due to its rarity. Improving the management of CIDP is a public health need that is an established priority (GTNDO priority, Rare Diseases Plan).

Because of the low level of proof of the available data and of the presented findings, the expected impact on morbidity/mortality is low. The impact on quality of life and on the healthcare system has not been documented.

TEGELINE provides an additional means of meeting the identified public health need. However, given the size of the population, it is not expected that TEGELINE will benefit public health in this indication.

The efficacy/adverse effects ratio is high.

This medicinal product is a first-line therapy.

There are alternative treatments (corticoid therapy, plasmapheresis).

The actual benefit of TEGELINE 50 mg/ml is substantial.

4.2. Improvement in actual benefit (IAB)

TEGELINE provides a minor improvement in actual benefit (IAB IV) in the management of patients with chronic inflammatory demyelinating polyradiculoneuropathy.

4.3. Therapeutic use

According to the French CEDIT¹⁵ and European^{16,17} recommendations, IV human immunoglobulins represent the first-line treatment for chronic inflammatory demyelinating polyradiculoneuropathy as well as corticoid therapy and plasma exchange.

The strategy comprises initial treatment and maintenance treatment.

Initial treatment:

- For mild symptoms with moderate discomfort during everyday activities, watchful waiting is recommended.
- Presence of moderate to severe disability with sensorimotor impairment: In such patients, IVIG (2 g/kg over 2-5 days) (level A) and corticoids (1 mg/kg or 60 mg/day of prednisolone) (level B) are the first-line treatments. The choice between one or the other of these treatments is made on the basis of the respective contraindications (good practice). Thus, in diabetic patients the treatment of choice is IVIG, which, unlike corticoid therapy, does not carry a risk of diabetes decompensation.
- For purely motor symptoms: IVIG is the treatment of choice. If corticoids are used, careful monitoring is necessary because of a risk of neurological deterioration (good practice).
- If IVIG or corticoid therapy proves ineffective, plasma exchange must be considered (level A).
- The patient must be central to the decision on the choice of treatment and must be aware of the advantages and disadvantages of the various treatment options (good practice).

Maintenance treatment:

- If the first-line treatment is effective, the treatment should be continued until the maximum benefit is achieved, then tailored according to individual response (good practice).
- For IVIG, once the clinical response is obtained, it is recommended:
 - to establish the minimum effective IVIG dose (good practice),
 - to reduce the IVIG cycles at shorter intervals to avoid neurological deterioration (every 2 to 6 weeks),
 - to reduce the IVIG dosage before extending the interval between treatment cycles in stabilised patients (good practice).

¹⁵ Comité d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT). Intravenous (IVIG) and subcutaneous (SCIG) normal human immunoglobulins. AP-HP appraisal of use in 2006. December 2007. AP-HP, Clinical policy management.

¹⁶ Hughes R.A. et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. European Journal of Neurology 2006; 13: 326-332

¹⁷ European Federation of Neurological Societies Guideline for the use of intravenous immunoglobulin in treatment of neurological diseases. European Journal of Neurology 2008; 15: 893-908

- Corticoids should be maintained at the initial dosage for 12 weeks before declaring them ineffective. If a response is shown, the dose should be gradually tapered down to the minimum effective dose over a period of 1 to 2 years.
- If the response to IVIG or corticoid therapy is considered inadequate by the doctor and by the patient, or if the maintenance dosage is too high, the addition of another immunomodulatory therapy may be considered. However, no immunomodulatory therapy has been validated in this indication by a controlled randomised study.

4.4. Target population

CIDP is a rare disease. Because of the absence of specific diagnostic tests and the probable existence of overlooked atypical forms¹⁸, its frequency is poorly established. Epidemiological data are, moreover, scarce^{19,20} and estimate the prevalence of CIDP at between 1 and 7.7 cases per 100,000. In the French population (2008 INED data), this corresponds to between 630 and 4850 patients.

4.5. Transparency Committee recommendations

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

Packaging: Appropriate for the prescription conditions.

¹⁸ Vallat J.M. et al. Diagnostic value of nerve biopsy for atypical chronic inflammatory demyelinating polyneuropathy: evaluation of eight cases. *Muscle Nerve* 2003; 27(4): 478-85.

¹⁹ Mygland Å. et al. Chronic polyneuropathies in Vest-Agder, Norway. *European Journal of Neurology* 2001, 8: 157-165

²⁰ Chiò A. et al. Idiopathic chronic inflammatory demyelinating polyneuropathy: an epidemiological study in Italy. *J Neurol Neurosurg Psychiatry* 2007; 78: 1349-1353