HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

9 May 2007

TEGELINE 50 mg/ml, powder and solvent for solution for infusion
Box of 1 10 ml glass vial containing 0.5g of Ig (CIP: 559 895.3)
Box of 1 50 ml glass vial containing 2.5g of Ig (CIP: 559 897.6)
Box of 1 100 ml glass vial containing 5 g of Ig (CIP: 559 898.2)
Box of 1 200 ml glass vial containing 10 g of Ig (CIP: 559 899.9)

Applicant : LFB BIOMEDICAMENTS

Human normal immunoglobulin

List 1
Medicinal product for hospital prescription only

Date of Marketing Authorisation: July 31, 1996
Date of Revision: July 4, 2006

Reason for request: Inclusion on the list of medicines approved for use by hospitals in the new indication: “treatment of multifocal motor neuropathy (MMN)”

Health Technology Assessment Division.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Human normal immunoglobulin

1.2. Indications

- Replacement therapy in:
  - Primary immunodeficiencies with hypogammaglobulinaemia or functional humoral immunodeficiency,
  - children with congenital AIDS and recurrent infections,
  - Secondary immunodeficiencies of humoral immunity, in particular:
    - Chronic lymphocytic leukaemia or myeloma, with hypogammaglobulinaemia associated with recurrent infections,
    - allogeneic bone marrow transplantation with hypogammaglobulinaemia associated with an infection.
- Immunomodulation:
  - Idiopathic thrombocytopenic purpura (ITP) in adults or children at high risk of bleeding or prior to undergoing a medical or surgical procedure, in order to correct the platelet count,
  - Birdshot retinochoroiditis,
  - Guillain-Barré syndrome in adults,
  - **Multifocal motor neuropathy (MMN).**
- Kawasaki disease.

1.3. Dosage

Multifocal motor neuropathy (MMN):

For induction of remission treatment, the dose of 2g/kg administered over 2 to 5 days and repeated every 4 weeks is to be maintained for 6 months.
The maintenance treatment dose is 2g/kg administered over 2 to 5 days. The interval between the TEGELINE administrations and the duration of maintenance treatment is adapted to the individual time to recurrence of symptoms in patients.
If there is no response,TEGELINE may be discontinued after a minimum of 3 months and a maximum of 6 months of treatment.

Indication	Dosage	Rate of injections
Multifocal motor neuropathy (MMN)	- initial dose: 2 g/kg over 2 to 5 days	every 4 weeks for 6 months
	- maintenance dose: 2 g/kg over 2 to 5 days	The interval between maintenance treatment administrations and duration is adapted to the individual time to recurrence of symptoms

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

J ANTI-INFECTIVES FOR SYSTEMIC USE

J06 IMMUNE SERA AND IMMUNOGLOBULINS

J06B IMMUNOGLOBULINS

J06BA IMMUNOGLOBULINS, HUMAN NORMAL

J06BA02 Immunoglobulins, human normal, for intravascular administration

2.2. Medicines in the same therapeutic category

TEGELINE is the only intravenous human immunoglobulin with Marketing Authorisation (MA) in the "multifocal motor neuropathy" indication.

2.3. Medicines with a similar therapeutic aim

The various therapeutic methods currently used focus on reducing inflammation and autoimmune reaction. They are generally based on corticosteroid treatment alone or combined with plasma exchanges or immunosuppressants (azathioprine, cyclophosphamide, cyclosporine, interferon β -1a or rituximab).

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Efficacy of intravenous immunoglobulins:

Four placebo-controlled, double-blind, cross-over studies documented the efficacy of intravenous immunoglobulins (IVIg) in multifocal motor neuropathy with conduction blocks: Azulay 1994[1]; Van den Berg 1995[2]; Federico 2000[3]; Léger 2001[4]. These studies were the subject of a systematic Cochrane[5] review in which the authors concluded the non-significant improvement in motor incapacity following IVIg administration (primary endpoint) and the significant improvement in muscle strength (secondary endpoint) in patients.

[1] Azulay JP, Blin O, Pouget J, Boucraut J, Bille-Turc F, Carles G, Serratrice G. Intravenous immunoglobulin treatment in patients with motor neuron syndromes associated with anti-GM1 antibodies: a double-blind, placebo-controlled study. *Neurology* 1994; 44: 429-432

[2] Van den Berg LH, Kerkhoff H, Oey PL, Franssen H, Mollee I, Vermeulen M, Jennekens FG, Wokke JH. Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1995 Sep; 59(3): 248-252

[3] Federico P, Zochodne DW, Hahn AF, Brown WF, Feasby TE. Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. *Neurology* 2000 Nov 14; 55(9): 1256-1262.Comment in: *Neurology*. 2000 Nov 14; 55(9): 1246-1247

[4] Léger JM, Chassande B, Musset L, Meininger V, Bouche P, Baumann N.Intravenous immunoglobulin therapy in multifocal motor neuropathy. A double-blind, placebo-controlled study. *Brain* 2001; 124: 145-153.

[5] Van Schaik IN, van den Berg LH, de Haan R, Vermeulen M. Intravenous immunoglobulin for multifocal motor neuropathy. (Cochrane Review). Cochrane Database Syst Rev 2005 Apr 18;(2):CD 004429

Efficacy of TEGELINE: **study LFB N°43-64-013**

A non-interventional, retrospective study based on the analysis of hospital case files of patients with motor neuropathy with conduction block (MMNCB) and treated with TEGELINE between 1st January 1995 and 15 February 2003.

Primary objective: Evaluate the efficacy and safety (short- and long-term) of TEGELINE treatment in patients with MMNCB.

Main inclusion criteria:

- Patients between 20 and 80 years of age, with a beginning motor deficit of a limb or deficit of at least 2 defined motor nerves with upper limb predominance.
- Duration of the disease > 6 months.
- The patient must have at least one defined conduction block and have been treated with at least one course of TEGELINE during follow-up.

Endpoints:

- Efficacy: responder rate after 6 months of treatment.

Responses were assessed on a MRC (Medical Research Council) score, evaluating muscle strength of the 8 weakest muscles (score range from 0 [no contraction] to 5 [normal strength]).
Response was defined as improvement by at least 1 score point for muscle strength for two muscles corresponding to the impaired motor nerves.

- Safety: nature, severity and frequency of adverse events.

In total, 41 patients were included in this study, 1 patient was excluded from the analysis due to a late diagnosis of amyotrophic lateral sclerosis (ALS).
The patient population of the study was composed in part of treatment-naive patients treated *de novo* with TEGELINE (sub-group 1, n = 22) and the remainder of patients previously treated with IVIg (sub-group 2, n = 18). Analysis of the primary endpoint was conducted only for sub-group 1; only 20 patients were evaluable (lack of initial data for 2 patients).

Results:

Efficacy:

In sub-group 1, 14 of 20 patients were considered as responders after 6 months of TEGELINE treatment. This rate of response, for which the 95% CI was [0.46; 0.88], was significantly different ($p < 0.0001$), according to the authors, from the rate of responses in a "historic" placebo group estimated at 20%[6].

Safety:

Of the adverse events observed:

- The most frequently reported were headache (68% of patients, n=27), allergic reaction (23%, n=9), arterial hypertension (18%, n=7) and nausea (18%).
- The least frequently reported were chills (8%, n=3), myalgia (5%, n=2) and anxiety (5%, n=2).

3.2. Conclusion

A Cochrane meta-analysis demonstrated the efficacy of intravenous immunoglobulins in improving muscle strength (secondary endpoint) in multifocal motor neuropathy.

A study of TEGELINE was also presented in the transparency file.

[6] Léger JM, Chassande B, Musset L, Meininger V, Bouche P, Baumann N. Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. Brain. 2001;124(Pt 1):145-53

The objective of this retrospective study was to evaluate the efficacy and safety of TEGELINE in 40 patients with multifocal motor neuropathy.
The primary endpoint for efficacy was defined as the responder rate to TEGELINE treatment after 6 months, in a population of "treatment-naïve" patients treated *de novo* with TEGELINE (sub-group 1), regardless of the number of treatments undertaken during this period.
The results achieved demonstrated that the rate of response rate on MRC score was significantly higher than the rate observed with "historic" placebo ($p<0.0001$) for sub-group 1.
However, in light of the absence of a prospective direct comparison of TEGELINE to placebo and of the small size of samples investigated, these results must be interpreted with caution to assess the true quantity of effect.
The most frequently observed adverse events corresponded to those observed with IVIg administration.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Multifocal motor neuropathy is a rare disease characterised by the development of disability and marked deterioration in quality of life.
The efficacy/undesirable effect ratio is high.
This medicinal product is intended to provide curative treatment.
This medicinal product is intended as first-line therapy.
There are alternative treatments.

Public health benefit:

Multifocal motor neuropathy (MMN) is a serious disease that represents a small public health burden due to its scarcity.
Improving MMN management falls within the scope of an identified public health priority (GTNDO priority, Rare Diseases plan).
Despite the insufficiency of the available data, TEGELINE is expected to have an impact on morbidity/mortality and quality of life. This impact cannot be quantified.
TEGELINE should, therefore, provide an additional response to the identified public health requirement.
Therefore, it is expected that TEGELINE will have a public health benefit in this indication. However, in light of the population size and the insufficiency of the demonstration, this benefit is low.

The actual benefit provided by TEGELINE in this indication is substantial.

4.2. Improvement in actual benefit:

The Transparency Committee considers that TEGELINE provides a substantial improvement in actual benefit (IAB II) in patients with multifocal motor neuropathy.

4.3. Therapeutic use[7]

Multifocal motor neuropathy with persistent conduction block (MMN) is a dysimmunity neuropathy characterised by a pure motor deficit that is asymmetric, multifocal, incipient and predominant in the upper limbs, and of chronic progression. In 80% of cases, onset of the disease occurs between 20 and 50 years of age, with a clear predominance in men (sex ratio M/F= 2.6:1). The disease usually declares itself in an upper limb.
Progress is unpredictable, as the impairment may be limited to one or two motor nerves or it may progress to affect other motor nerves of the contralateral upper limb, or even the lower limbs. In all cases, the motor deficiency is asymmetric, with multi-vessel distribution. It is generally accompanied by cramping and fasciculation, then, finally, by amyotrophy.

MMN does not usually respond to corticosteroid treatment and plasma exchanges that may, occasionally, worsen the patient's condition. On the other hand, IVIg treatments (2g/kg infused over 2 to 5 days) are the recommended first-line treatment, requiring repeated infusions, as they result in a rapid but temporary improvement in 70% of cases.
If IVIg treatment is found to be insufficiently effective, and/or if the disease worsens, the prescription of another immunomodulating treatment may be justified. Cyclophosphamide, cyclosporine, azathioprine, beta 1a interferon and rituximab are possible treatments, whose efficacy has not been shown in controlled randomised studies.

4.4. Target population

Epidemiological data indicate that the prevalence of the disease is estimated between 1 and 2/100,000 inhabitants[8]. Thus, the number of patients with MMN in France could lie between 600 and 1,200 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 new indication and at the posology in the Marketing Authorisation.

[7] www.orpha.net. Neuropathie motrice multifocale avec bloc de conduction.
[8] Nobile-Orazio, E, Cappeleri A, Priori A. Multifocal motor neuropathy: current concepts and controversies. Muscle and Nerve 2005;31/663-680