HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

6 April 2011

COPAXONE 20 mg/ml, solution for injection, pre-filled syringe
B/28 (CIP code: 363 840-1)

Applicant: SANOFI-AVENTIS FRANCE

Glatiramer acetate
ATC code: L03AX13

List I

Exception drug status
Initial prescription and renewal by neurology specialists only
Medicine requiring special monitoring during treatment.

Date of Marketing Authorisation and amendments (National procedure): 26 March 2004, 18 October 2010 (AE)

Reason for request:
Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use in the extension of indication "patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis".

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Glatiramer acetate

1.2. Indication

Glatiramer acetate is indicated for the reduction in frequency of relapses in ambulatory patients (i.e. who can walk unaided) with relapsing-remitting multiple sclerosis (MS). In clinical trials this was characterised by at least two attacks of neurological dysfunction over the preceding two-year period. Glatiramer acetate has not been shown to have any beneficial effect on disease progression.

Glatiramer acetate is not indicated in primary or secondary progressive MS.

This medicinal product is indicated in patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis.

1.3. Pharmacodynamic properties

Single clinical event suggestive of MS:
[…]

In all cases, treatment should only be considered for patients classified as being at high risk of clinically definite multiple sclerosis (McDonald criteria revised in 2005[1]).

a) Patients with a monosymptomatic presentation are considered to be at high risk from the following MRI criteria:

Criteria for dissemination in space

Three of the following criteria:
- At least one Gd-enhancing T1 lesion or 9 hyperintense T2 lesions (if no Gd-enhancing lesion)
-- At least one infratentorial lesion
- At least one juxtacortical lesion
- At least 3 periventricular lesions

Note: one spinal cord lesion is considered to be equivalent to one infratentorial lesion. A Gd-enhancing spinal cord lesion may be counted as a Gd-enhancing brain lesion. A spinal cord lesion may also be counted towards the required number of T2 brain lesions.

Criteria for dissemination in time

There are two ways of determining dissemination in time:
- Detection of a Gd lesion at least three months after onset of the initial clinical attack, at a site different from the initial attack.
- Detection of a new T2 lesion at any time after a reference MRI scan performed at least 30 days after the initial clinical attack.

b) In patients with multifocal presentation (at least two clinical sites), only the criteria for dissemination in time are required.

1 Polman CH et al. Diagnostic Criteria for multiple Sclerosis: 2005 Revisions to the "McDonald Criteria". Ann Neurol 2005; 58: 840-6.

1.4. Dosage

The recommended dosage in adults is 20 mg of glatiramer acetate (one 1 mL pre-filled syringe) administered as a subcutaneous injection once daily.
Glatiramer acetate should be initiated and renewed under the supervision of a neurologist.
At the present time, it is not known for how long the patient should be treated.
A decision concerning long-term treatment should be made on an individual basis by the treating doctor.

Use in children and adolescents:
No prospective, randomised, controlled clinical trials or pharmacokinetic studies have been conducted in children or adolescents.
However, limited published data suggest that the tolerance profile of COPAXONE in adolescents from 12 to 18 years of age receiving 20 mg of glatiramer acetate subcutaneously every day is similar to that seen in adults.
There is not enough information available on the use of glatiramer acetate in children below 12 years of age and glatiramer acetate should therefore not be used in this population.

Use in the elderly:
Glatiramer acetate has not been specifically studied in the elderly.

Use in patients with impaired renal function:
Glatiramer acetate has not been specifically studied in patients with renal impairment.
Patients should be instructed in self-injection techniques. They should be supervised by a healthcare professional the first time they self-inject and for 30 minutes afterwards. A different site for injection should be chosen every day, so this will reduce the chances of any irritation or pain at the site of the injection. Sites for self-injection include the abdomen, arms, hips and thighs.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (WHO, 2011)

L : Antineoplastics and immunomodulating agents
L03 : Immunostimulants
L03A : Immunostimulants
L03AX : Other immunostimulants
L03AX13 : Glatiramer acetate

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

Interferon beta-1b - BETAFERON, EXTAVIA (Extension of indication: 01 June 2006)
Interferon beta-1a - AVONEX (Extension of indication: 07 May 2002)

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The dossier submitted contains the results of the comparative, placebo-controlled PreCISe trial performed in patients with a first clinical episode suggestive of multiple sclerosis.

3.1.1 PreCISe trial - glatiramer acetate versus placebo

The PreCISe trial[1], a randomised, double-blind trial of superiority, compared the efficacy and tolerance of glatiramer acetate (20 mg/day subcutaneously) with placebo in patients with a single focal demyelinating event within the last 90 days, accompanied by brain lesions (at least two cerebral lesions ≥ 6 mm diameter on T2-weighted MRI) compatible with MS.

The primary efficacy endpoint was time to onset of clinically definite multiple sclerosis (CDMS) according to the Poser criteria[2] at three years. The protocol was amended to include an intermediate analysis on data accumulated from 80% of the study exposure.
Secondary endpoints included the percentage of patients who developed CDMS.

Four hundred and eighty-one patients, mean age = 31 years, were randomly assigned to receive glatiramer acetate (n=243) or placebo (n=238). 44% of patients had at least one Gd-enhancing T1 lesion and 84% had at least nine T2 lesions. Corticosteroids had been used for the first attack in 64% of patients.

Mean duration of exposure to treatment was about 20 months on the date of the intermediate data analysis; 13% of patients in the placebo group and 16% in the glatiramer acetate group completed the three-year monitoring period.

According to a Kaplan-Meier estimate, the time for 25% of patients to convert to CDMS was prolonged by a mean of 386 days under COPAXONE (722 days) compared with placebo (336 days) (HR = 0.55, 95% CI [0.40-0.77]). The relative reduction in risk of onset of CDMS was 45%.
42.9% of patients in the placebo group and 24.7% of patients in the glatiramer acetate group developed CDMS.

A posthoc subgroup analysis was performed on patients at high risk of developing CDMS (at least one Gd-enhancing T1 lesion and at least nine T2 lesions on MRI). 28% of patients in the glatiramer acetate group (n=92) and 50% of patients in the placebo group (n=101) had developed CDMS at 2.4 years.

Sixty-two patients stopped treatment prematurely before the end of the double-blind period, i.e. 16% of patients (39/243) in the glatiramer acetate group and 9.7% of patients (23/238) in the placebo group. The most common reasons for dropout were: glatiramer acetate group: (patient's decision 15, adverse event 14); placebo group: (patient's decision 12, adverse event 4).

1 Comi G et col. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomized, double-blind, placebo-controlled trial. Lancet 2009; 374: 1503-11.

2 Poser et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocol. Ann Neurol 1983; 13: 227-31.

Tolerance data

54% of patients in the COPAXONE group and 63% of patients in the placebo group were exposed to treatment for less than 2 years. The most commonly-reported adverse events were injection-site reactions (56% of patients in the glatiramer acetate group compared with 24% in the placebo group) and immediate post-injection reactions (19% versus 5% of patients).
The other adverse events reported included: headache (19.8% versus 17.7%), infections (12.8% versus 10.1%), peripheral vasodilatation (11.5% versus 2.9%), dyspnoea (7.4% versus 1.3%), back pain (10.3% versus 7.1%), chest pain (6.6% versus 1.7%), nausea (6.6% versus 4.2%), vomiting (5.8% versus 2.1%), lymphadenopathy (5.3% versus 0.4%), flu-like syndrome (4.1% versus 0.8%), pruritus (3.7% versus 1.3%) and erythema (3.7% versus 1.3%). At least one severe event was reported in 5.0% of patients in the COPAXONE group and 8.2% in the placebo group.

3.2. Adverse Effects - United States postmarketing data

The most common adverse effects of glatiramer acetate are injection-site reactions. Immediate post-injection reactions are common, and usually transient. More severe adverse effects may occur, such as lipoatrophy and lymphadenopathy.

The first marketing authorisation for COPAXONE was issued in 1996 (Israel and the United States). Data from three pivotal studies of relapsing-remitting MS were collected from 269 patients receiving COPAXONE and 271 patients receiving placebo. The most common adverse effect was injection-site reaction (82.5% versus 48% on placebo). Immediate post-injection reactions were reported in 41% of patients (versus 20% on placebo).

COPAXONE is currently registered in 32 countries. Tolerance data obtained from clinical trials and the periodic tolerance update reports (PSUR) for COPAXONE covering the period 01 December 2001 to 30 November 2007 confirm its known tolerance profile. No changes to the Summary of Product Characteristics have been required. No new recommendations have been made for specific clinical or laboratory monitoring.
As at 31 August 2009, more than 162 000 patients have been exposed, i.e. more than 929 400 patient-years.

3.3. Conclusion

One double-blind, randomised study (PreCISe) compared the efficacy of 20 mg glatiramer acetate administered subcutaneously every day with that of placebo in patients with a single focal demyelinating event within the last 90 days, accompanied by brain lesions compatible with MS. The data were obtained from an intermediate analysis, with a mean of 20 months exposure to the drug. Thirteen percent (13%) of patients in the placebo group and 16% in the glatiramer acetate group completed the three-year monitoring period.

Time to onset of clinically definite multiple sclerosis (CDMS) was prolonged by a mean of 386 days with COPAXONE (722 days) compared with placebo (336 days): HR = 0.55, 95% CI [0.40-0.77]. This period could only be calculated in 25% of patients in each of the treated groups as fewer than 50% patients had converted to CDMS at the time of analysis. There was a 45% relative reduction in risk of onset of CDMS in these patients.
42.9% of patients in the placebo group and 24.7% of patients in the glatiramer acetate group developed CDMS. In the subgroup of patients at high risk of conversion to CDMS (at least one Gd-enhancing T1 lesion and at least nine T2 lesions on MRI), the percentages were 50% versus 28% at 2.4 years.

The most commonly reported adverse events with glatiramer acetate were injection-site reactions (56% with glatiramer acetate versus 24% with placebo), immediate post-injection reactions (19% versus 5% of patients, including vasodilatation, tightness of the chest, dyspnoea, palpitation or tachycardia), vomiting (5.8% versus 2.1%), lymphadenopathy (5.3% versus 0.4%) and flu-like syndrome (4.1% versus 0.8%).

Glatiramer acetate was not compared with interferon beta in this indication.

The impact of early treatment with COPAXONE on disease progression and the long-term course of the disease is unknown.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Multiple sclerosis is an incapacitating, progressive, chronic neurological disorder. It involves the selective, chronic inflammation and demyelinisation of the central nervous system. It has many manifestations, including sensory and motor disorders, sensory deficits, bladder and sphincter disorders, sexual problems, cognitive function disorders and mood disorders. These problems may considerably reduce patients' autonomy and adversely affect their quality of life. The disease varies greatly in severity, from forms causing little incapacity to forms leading to severe disability within a few years.

COPAXONE is a medicinal product intended to prevent attacks of MS.

In the short term, the efficacy/adverse effects ratio for this proprietary medicinal product in the extended indication is low. The efficacy/adverse effects ratio in the longer term has not yet been established.

Interferon beta is also indicated in patients who have experienced a well-defined first clinical episode and are considered to be at high risk of developing clinically definite multiple sclerosis.

Public health benefit

MS is a moderate public health burden. The public health burden of patients who have experienced a single clinical episode is low because of their small number.

Improvement in the treatment of MS is a public health need which is an established priority (French 2004 Law on Public Health).

In view of the available data, this proprietary medicinal product is not expected to have any impact in terms of morbidity, mortality or quality of life, compared with the available treatments.

In view of the available data, the degree of impact of COPAXONE on morbidity (time to onset of CDMS) is small. The long-term effects of COPAXONE are not known. Globally, this proprietary medicinal product is not expected to have any impact on the population in terms of morbidity, mortality or quality of life, compared with the available treatments.

The proprietary medicinal product COPAXONE is therefore unlikely to be able to offer any additional response to the identified public health need.

Consequently, this proprietary medicinal product is not expected to benefit public health.

The actual benefit of COPAXONE is substantial.

4.2. Improvement in actual benefit (IAB)

COPAXONE does not provide any improvement in actual benefit (IAB V) in the treatment of patients who have experienced a single clinical episode and who are considered to be at high risk of developing clinically definite multiple sclerosis.

4.3. Therapeutic use

There are three main types of progressive multiple sclerosis, i.e. relapsing-remitting (RRMS), secondary progressive and primary progressive.

Disease onset takes the form of attack and remission in about 85% of cases (remitting at onset) and is primary progressive with or without further attacks, but with no relapsing-remitting phase, in the remaining cases (15%). In the case of relapsing-remitting forms at onset, the second relapse occurs during the first two years in 50% of patients. The estimated median

time to onset of secondary progressive MS in patients with the relapsing-remitting form at onset is between 15 and 19 years according to the series.
Multiple sclerosis which leads to disability in a short period of time is called aggressive. It may be characterised by a high frequency of attacks (at least two attacks with sequelae) or progression by two points on the Expanded Disability Status Scale (EDSS) scale, in the previous 12 months.

Interferon treatment remains the first-line disease-modifying treatment in RRMS. Glatiramer acetate is also indicated in these patients. These medicinal products have not shown that they have a beneficial effect on disease progression in the long-term. They have different tolerance profiles.
Interferon beta-1b and interferon beta-1a IM are indicated in patients with a first clinical event who are considered to be at high risk of developing clinically definite multiple sclerosis (CDMS). Glatiramer acetate is an alternative form of treatment in this indication.
None of these treatments has a Marketing Authorisation in primary progressive MS.

4.4. Target population[1]

The target population for COPAXONE in this indication consists of patients who have experienced one clinical episode and who are considered to be at high risk of developing clinically definite MS.
The estimated incidence of multiple sclerosis is 2000 new cases a year,[2] 80-85% of which involve the remitting form of the disease. Based on these data, the highest estimate of the population likely to receive COPAXONE in this indication is 1 700 patients.

4.5. Transparency Committee recommendations

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

4.5.1 Packaging

The Committee points out that in accordance with its deliberations on 20 July 2005, it recommends that pack sizes be standardised to 30 days' treatment for treatments lasting one month.

4.5.2 Reimbursement rate: 65%

1 White paper on Multiple Sclerosis - Steering Committee of the French Convention on Multiple Sclerosis - April 2006

2 "Multiple sclerosis", French Ministry of Health Rare Diseases plan (DGS/GTNDO) 13 March 2003.