TRANSPARENCY COMMITTEE

OPINION

9 May 2012

ANAPEN 0.50 mg/0.3 ml, solution for injection in pre-filled syringe
1 pre-filled syringe (glass), box of 1 auto-injector (CIP code: 34009 217 493 9 7)

Applicant: BIOPROJET PHARMA

Adrenaline
ATC code: C01CA24

List I

Date of European Marketing Authorisation: 14 October 2011
(Abbreviated MA procedure, mutual recognition)

Reason for request: Inclusion on the list of medicines refundable by National Insurance and approved for hospital use (addition to range).

Medical, Economic and Public Health Assessment Division
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Adrenaline
Excipients: sodium metabisulfite (E223), sodium chloride

1.2. Indication

“Emergency treatment for acute allergic reactions (anaphylaxis) caused by peanuts or other foods, drugs, insect bites or stings, and other allergens as well as exercise-induced or idiopathic anaphylaxis.”

1.3. Dosage

“The effective dose is typically in the range 0.005-0.01 mg/kg but higher doses may be necessary in some cases.

Use in adults: the usual dose is 300 micrograms.

An overweight adult may require a dose of 500 micrograms of ANAPEN to reverse the effects of an acute allergic reaction.

In some circumstances a single dose of adrenaline (epinephrine) may not completely reverse the effects of an acute allergic reaction and for such patients a repeat injection may be given after 10-15 minutes.

Use in children:
ANAPEN 0.50 mg/0.3 ml, solution for injection in pre-filled syringe, is not recommended for use in children.

Method and route of administration:

ANAPEN consists of a pre-filled syringe of adrenaline (epinephrine) contained in an auto-injection device. The whole is referred to as an auto-injector.

Use only by the intramuscular route.

ANAPEN auto-injector is intended for immediate self administration by a person with a history of anaphylaxis. It is designed to deliver a single dose of 500 micrograms (0.3 ml) adrenaline (epinephrine). For stability reasons 0.75 ml is left in the syringe after use but the unit cannot be used again and should be safely discarded.
2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2012)

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<thead>
<tr>
<th>ATC Code</th>
<th>Description</th>
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<tr>
<td>C</td>
<td>Cardiovascular system</td>
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<td>C01</td>
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<td>Cardiac stimulants excluding cardiac glycosides</td>
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<td>C01CA</td>
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<tr>
<td>C01CA24</td>
<td>Epinephrine (adrenaline)</td>
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2.2. Medicines in the same therapeutic category

Other autoinjectable adrenaline-based proprietary medicinal products (marketed):

ANAPEN, solution for IM injection¹ (in adults and in children weighing more than 15 kg i.e. about 4 years of age). Two dosages are reimbursable: 0.15 mg/0.3 ml and 0.30 mg/0.3 ml.

NB: ANAHELP 1 mg/1 ml, solution for SC and IM injection, has not been on the market since September 2009.²

3. ANALYSIS OF AVAILABLE DATA

The MA was granted in an abbreviated procedure. No clinical efficacy and/or safety study has been carried out specifically with this new dosage of ANAPEN.

¹ ANAPEN pen is supplied as a pre-filled syringe contained in an auto-injection device and can be stored at room temperature (not exceeding + 25°C) in the original primary packaging to protect the medicine from light.

² This proprietary medicinal product was withdrawn from the market on 1 April 2009. Abbreviated MA of 18 August 2010. ANSM website consulted on 22 May 2012.
4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Anaphylactic shock is a life-threatening condition.

ANAPEN is a first-line curative treatment the efficacy/safety ratio of which is high.

Public health benefit

- Given the absence of predisposing factors and the wide variation in individual reactions to possible allergens, the burden of anaphylactic shock cannot be assessed.
- The treatment of anaphylactic shock and the prevention of its consequences are a public health need.
- The intramuscular auto-injection of adrenaline in the event of anaphylactic shock has an important impact on morbidity and mortality and can reduce the use of emergency care services.
- This new dosage of the proprietary medicinal product ANAPEN is a useful addition to the range for overweight adult patients. This dosage is therefore not expected to have any additional impact on morbidity and mortality in therapeutic use.
- Consequently, the proprietary medicinal product ANAPEN is not expected to benefit public health.

There is no other adrenaline auto-injector currently on the market in France.

The actual benefit of ANAPEN 0.5 mg/0.3 ml is substantial.

4.2. Improvement in actual benefit (IAB)

This new dosage of ANAPEN is an addition to the range; it is suitable for prescription use in overweight adult patients. It does not provide any improvement in actual benefit (level V IAB) on this account.

4.3. Therapeutic use

The treatment of anaphylactic shock is a medical emergency. Adrenaline is the medicine of choice for reversing allergic or idiopathic hypersensitivity reactions or exercise-induced anaphylaxis. One of the characteristics of this condition is its rapid reversibility if treatment is started early and in the right doses. All persons with a history of anaphylactic shock or a high degree of risk because of an atopic condition should be given an adrenaline auto-injector system. The ANAPEN injection must be given intramuscularly, without delay, on the appearance of warning signs and symptoms of anaphylactic shock.

The effective dose is typically in the range 0.005-0.01 mg/kg but higher doses may be necessary in some cases. ANAPEN 0.5 mg/30 ml is a presentation suitable for overweight adult patients. Its use is not recommended for children and the usual dose in adults is 300 micrograms.
4.4. Target population

The target population for ANAPEN consists of patients with a history of anaphylactic shock or a high degree of risk because of an atopic condition.

Their numbers can be estimated fairly inaccurately on the basis of the following theories:
- food allergies and hymenoptera stings account for the vast majority of allergies that may require the use of adrenaline.
- prevalence of food allergies: between 2.1% and 3.8% in the general population (document from the French Food Safety Agency (AFSSA), January 2002). Of these, 10% to 20% develop a severe form that justifies having an adrenaline auto-injector close at hand.
- prevalence of allergies to hymenoptera stings: about 1% in the general population. Of these, the proportion likely to develop a severe form is not known exactly (figure thought to be between 10% and 20%)
- Persons with a history of anaphylactic shock are included in the population thus defined. The target population is estimated to be between 180,000 and 580,000 persons.\(^3\)

Assuming that 80% of the patients concerned have a weight of at least 60 kg and given that prescriptions for ANAPEN 0.3 mg/0.3 ml account for nearly 70% of all prescriptions for ANAPEN, the target population for this new dosage of ANAPEN 0.5 mg/0.3 ml would be between 100,000 and 325,000 persons.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion of ANAPEN 0.5 mg/0.3 ml, solution for injection in a pre-filled syringe (B/1) 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 indication and at the dosage in the Marketing Authorisation.

4.5.1. Packaging: appropriate for the prescription conditions.

However, this new packaging still does not meet the Committee’s initial request since:
- The patient needs to have two syringes. “In some circumstances a single dose of adrenaline (epinephrine) may not completely reverse the effects of an acute allergic reaction and for such patients a repeat injection may be given after 10-15 minutes” (SPC). ANAPEN is available in a packaging containing two auto-injectors. In its reinclusion opinion of 18 March 2009, the Committee recommended making available the ANAPEN pack of 2 auto-injectors.
- The Committee had also noted the absence of a presentation suitable for children weighing less than 15 kg (about 4 years of age). “A form capable of delivering 0.10 mg of adrenaline would be useful to cover this age group.”

4.5.2. Reimbursement rate: 65%.

\(^3\) Cf. Inclusion opinion for EPIPEN of 27 May 2009.