HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

27 May 2009

EPIPEN 0.15 mg/0.3 mL, solution for injection in prefilled syringe (Auto-Injector)
B/1, blister strips (PP/Alu) (CIP code: 388 033-2)
B/2, blister strips (PP/Alu) (CIP code: 388 034-9)

EPIPEN 0.30 mg/0.3 mL, solution for injection in prefilled syringe (Auto-Injector)
B/1, blister strips (PP/Alu) (CIP code: 388 030-3)
B/2, blister strips (PP/Alu) (CIP code: 388 032-6)

Applicant: MYLAN

Adrenaline

List I

ATC code: C01CA24

Date of Marketing Authorisation (national procedure): 3 September 2008.

Reason for request: Inclusion on the list of drugs reimbursed by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Adrenaline

1.2. Indication

"Emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, peanuts or other foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis".

1.3. Dosage

"EPIPEN should only be injected intramuscularly into the anterolateral aspect of the thigh, and not into the buttock. The injection area may be massaged gently for 10 seconds after administration. EPIPEN 0.15 mg/0.3 mL or 0.30 mg/0.3 mL Auto-Injectors are intended for immediate self-administration by individuals with a history of anaphylactic reaction. They are designed to deliver a single 150 or 300 µg (0.3 mL) dose of adrenaline. For reasons of stability, an unused volume of 1.7 mL remains in the syringe after use. However, the device should not be reused and should be disposed of, taking the appropriate safety precautions.

The usual effective dose is between 0.005 and 0.01 mg/kg, but higher doses may be needed in some circumstances.

Use in children
The appropriate dose is 150 µg (EPIPEN 0.15 mg/0.3 mL) or 300 µg (EPIPEN 0.30 mg/0.3 mL) of adrenaline depending on the child's body weight and the doctor's decision. A further injection may be required in children with a high bodyweight.

The product should not be used in children weighing under 15 kg except in a life-threatening situation or at the doctor's decision, as doses below 150 µg adrenaline cannot be administered accurately to these children.

Use in adults
The usual dose is 300 µg. A further injection may be required in patients with a high body weight.

In some situations, a single dose of adrenaline may not be sufficient to reverse the effects of an acute allergic reaction. In this case, a further dose may be injected after 10-15 minutes.

The patient must have two syringes. EPIPEN comes in packs of two auto-injectors".

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

C	Cardiovascular system
C01 :	Cardiac therapy
C01C :	Cardiac stimulants excluding cardiac glycosides
C01CA :	Adrenergic and dopaminergic agents
C01CA24 :	Epinephrine

2.2. Medicinal products in the same therapeutic category

Devices containing adrenaline for self-injection:
In adults and children weighing more than 15 kg (about 4 years):
- ANAPEN, solution for IM injection[1]
Two dosages: 0.15 mg/0.3 mL and 0.30 mg/0.3 mL

In adults and children aged over 6 years:
- ANAHELP 1 mg/1 mL, solution for SC or IM injection[2]

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

No clinical trials of efficacy and/or safety are available which have compared EPIPEN to other preparations containing adrenaline.

Comparison of EPIPEN with other available medicinal products is therefore limited to analysis of their technical characteristics (particularly with regard to the auto-injector).

3.2. Adverse effects

Adverse effects depend on the patient's sensitivity and the dose administered. The anticipated safety profile of EPIPEN is comparable to that of other preparations containing adrenaline:
At low dose, the common adverse effects are: palpitations, tachycardia, sweating, nausea, vomiting, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, apprehension, nervousness and anxiety.

At high dose or in patients sensitive to adrenaline, the adverse effects are: arrhythmia (ventricular fibrillation/cardiac arrest), sudden rise in blood pressure (occasionally causing brain haemorrhage), or even vasoconstriction (e.g. in the skin, mucosa or kidneys).

EPIPEN and ANAPEN contain sodium metabisulfite and may cause allergic reactions which may include anaphylactic symptoms, or may even be life-threatening.
Mild asthma may also occur in some patients who are sensitive to sulfite.

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[1] ANAPEN pens come as prefilled syringes inside an auto-injector device and may be stored at ambient temperature (not exceeding + 25°C) in the original primary pack to protect the medicinal product from light.
[2] ANAHELP comes in the form of an emergency kit for prevention and treatment of anaphylactic shock:
- 1 sterile syringe for self-injection
- 1 four-position piston for delivery of 0.25 mL, 0.50 mL, 0.75 mL or 1 mL, depending on the number of tabs broken (the piston cannot be used unless screwed onto the black tip contained in the syringe).
ANAHELP should be stored between +2°C and +8°C and can be c arried at ambient temperature[2].

3.3. Conclusion

EPIPEN is the second medicinal product to be introduced on the market in the form of a prefilled syringe of adrenaline in an auto-injector device for intramuscular use, for the treatment of anaphylactic shock.

The data supplied do not demonstrate any additional clinical benefit of EPIPEN compared with other preparations of adrenaline for self-injection.

ANAPEN and EPIPEN have different self-injection devices.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Anaphylactic shock is a life-threatening condition. EPIPEN is a first-line curative therapy with a substantial efficacy/adverse effects ratio. For children aged 4-6 years there is only one alternative therapy, i.e. ANAPEN.

Public health benefit

It is not possible to assess the burden resulting from anaphylactic shock, in view of the absence of predisposing factors and the wide variation in individual reactions to possible allergens. Treatment of anaphylactic shock and prevention of its consequences is a public health need. In the event of anaphylactic shock, intramuscular self-injection of adrenaline has a major impact on morbidity and mortality and reduces the use of emergency care services. EPIPEN has no additional impact compared with the adrenaline auto-injectors already on the market. EPIPEN is therefore a new alternative treatment option.
Consequently, no public health benefit is anticipated for the medicinal product EPIPEN.

The actual clinical benefit of EPIPEN is substantial.

4.2. Improvement in actual benefit (IAB)

EPIPEN does not provide any improvement in actual benefit (IAB level V) over ANAPEN. EPIPEN is a useful additional form of treatment.

4.3. Therapeutic use

Treatment of anaphylactic shock is a clinical emergency.

Treatment may require admission to hospital in the intensive care unit for appropriate resuscitation measures.

Adrenaline is a sympathomimetic amine; it is a catecholamine secreted naturally by the adrenal glands in response to exhaustion or stress. It is the drug of choice[3] for treating allergic or idiopathic hypersensitivity reactions and exercise-induced anaphylaxis.

One of the characteristics of anaphylactic shock is its rapid reversibility if treatment is started early and at the right doses. Anyone with a history of anaphylactic shock or a high degree of risk because of an atopic condition should benefit from an adrenaline auto-injector system.

[3] Adrenaline has a vasoconstrictrive action induced by major stimulation of alpha-adrenergic receptors. This allows it to control vasodilatation and excessive vascular permeability which lead to loss of intravascular fluid and hypotension, the predominant pharmacotoxic symptoms responsible for anaphylactic shock. The stimulant action of adrenaline on beta-adrenergic bronchial receptors leads to powerful bronchodilatation which reduces respiratory wheeze and dyspnoea. Adrenaline also alleviates pruritus, urticaria and angioedema associated with anaphylaxis (SPC).

EPIPEN 0.15 mg/0.3 mL or 0.30 mg/0.3 mL Auto-Injectors are intended for immediate self-administration by individuals with a history of anaphylactic reaction. The Auto-Injector is designed to deliver a single dose. An EPIPEN injection should be performed into the muscle, without delay, as soon as precursor signs and symptoms of anaphylactic shock appear. These signs and symptoms may occur within a few minutes of exposure to the allergen. They usually manifest as urticaria, hot flushes or angioedema. More severe reactions may affect circulatory and pulmonary systems.
In some situations, a single dose of adrenaline may not be sufficient to reverse the effects of an acute allergic reaction. In this case, a further dose may be injected after 10-15 minutes. The patient must therefore have two syringes.
EPIPEN is a useful additional form of treatment (having a second Auto-injector also helps to reduce the risk of disruption of supplies of these emergency drugs).

4.4. Target population

The target population for EPIPEN is defined as patients with a history of anaphylactic shock or a high degree of risk because of an atopic condition.

Quantitative estimate:
The target population has been increasing for the last 10 years or so; its size may be estimated approximately on the basis of the following hypotheses:
- The great majority of allergies that may require adrenaline are food allergies and hymenoptera stings (reason given in more than 95% ATU requests for ANAPEN).
- The prevalence of food allergy is between 2.1% and 3.8% of the general population (AFSSA document, January 2002). 10%-20% of these individuals develop a severe form requiring them to keep an adrenaline auto-injector with them at all times.
- The prevalence of allergy to hymenoptera stings is about 1% in the general population. The proportion of this population that may develop a severe form is not known with any accuracy (a hypothetical figure is between 10% and 20%).
- Individuals with a history of anaphylactic shock are included in the population defined above.

On the basis of these observations, the estimated target population is between 180 000 and 580 000 individuals.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for use by hospitals and various public services in the indications and at the dosage given in the Marketing Authorisation.

Packaging: The packaging is appropriate for the prescription conditions given in the Marketing Authorisation.

The patient should carry two syringes. A pack of two Auto-Injectors is available.

Reimbursement level: 65%