NOTIFICATION TO THE CHMP/EMEA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
FAX NUMBER –44 20 75237051

This notification is an official referral under Article 31 of Directive 2001/83/EC to the CHMP made by the United Kingdom (UK):

Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s)	All adrenaline auto injectors (AAIs) containing adrenaline solution in a pre-filled delivery system for self-administration. In the UK, the following products were identified: EpiPen 300 microgram auto injector PL 15142/0245 EpiPen Jnr 150 microgram auto injector PL 15142/0246 Jext 150 microgram auto injector PL 10085/0052 SE/H/908/01/DC Jext 300 microgram auto injector PL 10085/0053 SE/H/908/02/DC Emerade 150 microgram auto injector PL 42457/0001 SE/H/1261/001/DC Emerade 300 microgram auto injector PL 42457/0002 SE/H/1261/001/DC Emerade 500 microgram auto injector PL 42457/0003 SE/H/1261/001/DC
Active Substance(s)/Therapeutic class	Adrenaline or adrenaline tartrate ATC code: C01CA24

Applicant(s)/Marketing Authorisation Holders for the UK

- MEDA Pharmaceuticals Ltd
- ALK-Abelló A/S
- Namtall AB

The above mentioned Member State considers that it is in the interest of the Union to refer the above mentioned adrenaline auto injectors (AAIs) containing adrenaline solution in a pre-filled delivery system for self-administration.

Pharmacotherapeutic class: Cardiac stimulants excluding cardiac glycosides, adrenergic and dopaminergic agents.

ATC code: C01CA24.

Background

Anaphylaxis is a severe, life-threatening systemic reaction that can affect all ages. The clinical syndrome may involve multiple target organs, including skin, respiratory, gastrointestinal, and cardiovascular systems. The essential underlying mechanism is the presence of biologically active chemical mediators such as histamine and tryptase released from mast cells or basophils.

When anaphylaxis is fatal, death usually occurs very soon after contact with the trigger. From a case-series, fatal food reactions cause respiratory arrest typically after 30–35 minutes; insect stings cause collapse from shock after 10–15 minutes; and deaths caused by intravenous medication occur most commonly within five minutes. Studies of fatal and near-fatal anaphylaxis in humans delineate risk factors for anaphylaxis such as pre-existing asthma, a current asthma attack, food allergies (particularly peanuts, tree nuts and shellfish), reaction to trace amounts of foods and use of non-selective β-blockers.

The MHRA has undertaken a review of all authorised adrenaline auto-injectors [redacted]

The [redacted] findings and evidence provided by expert immunologists led [redacted] to recommend a review of four areas:

1. The need to contact emergency services after administration of an auto injector even if the symptoms are abating.
2. The most effective site for injection and clarity of instructions.
3. The most appropriate auto injector needle length for ensuring intramuscular (IM) delivery of the adrenaline injection rather than subcutaneous (SC).
4. The optimal position for transporting a patient following an anaphylactic event.

The MHRA was asked to review available information in order to evaluate points 2 and 3 since evidence suggested that the needle had not penetrated beyond the subcutaneous layer of fat. The MHRA met with all MAHs to advise them of the review and ensure that all relevant information was considered.

Outcome of the MHRA review

All the auto injector products approved in the UK have been authorised on the basis of bibliographic data relating to the known efficacy and safety of intramuscular (IM) adrenaline by manual needle and syringe in the treatment of anaphylaxis. The SmPC of all the autoinjectors state that the route of administration is IM as this elicits the most rapid response. However, a key finding of the review was that there is no robust

evidence that the devices deliver the adrenaline intramuscularly in all patients. Variability in skin-to-muscle depth, gender, needle length and the device mechanism itself are important factors which determine whether the route of delivery is IM or subcutaneous (SC).

Published data based on porcine cadaver models provide information on the likely site of delivery of the injection but these models have shortcomings and are of questionable relevance to in vivo use in humans. Pharmacokinetic data indicate that subcutaneous administration is associated with significantly longer T_{max} (34 - 40 mins in adults) for adrenaline when compared with intramuscular administration (10-20 mins in adults) and thus might be less effective in the treatment of an anaphylactic event given that the reported time course of collapse from shock and/or respiratory arrest is 10 to 35 minutes. Hence the intramuscular route of delivery is preferred in the acute treatment of anaphylactic episodes wherever possible. In view of the paucity of information on the site of administration/absorption and its potential significance for the efficacy of the products used in a lifesaving situation, the MHRA proposes that a European assessment is performed of the evidence that the devices deliver the adrenaline intramuscularly in all patients. In addition, an assessment should be conducted on whether the Product Information contains clear and detailed instructions for use.

As the products authorised in the UK which were the subject of the review are also authorised in other member states either nationally or via the decentralised procedure, the UK considers that it is in the interest of the Union to refer adrenaline autoinjector products to the Committee for Medicinal Products for Human Use (CHMP) and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn.

Signed [redacted] Date 2/4/2014

[redacted]