LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Nepipe Junior, Nepipe (former Adrenalin MEDA) (adrenaline)

SE/H/1287/01-02/DC

This module reflects the scientific discussion for the approval of Nepipe Junior and Nepipe. The procedure was finalised at 2013-07-24. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Meda AB has applied for a marketing authorisation for Nepipe Junior and Nepipe, solution for injection in pre-filled pen, 150 micrograms and 300 micrograms. The application is submitted according to Article 10a of Directive 2001/83/EC, i.e. a well established use application. The active substance is adrenaline. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Nepipe Junior and Nepipe are presented in the form of a solution for injection containing 150 microgram or 300 microgram of adrenaline. The excipients are hydrochloric acid, sodium chloride, sodium metabisulfite and water. The solution is filled in a pen.

II.2 Drug Substance

Adrenaline has a monograph in the Ph Eur.

Adrenaline is a white or almost white crystalline powder. It is practically insoluble in water, in ethanol (96%) and in methylene chloride. It dissolves in hydrochloric acid. The structure of adrenaline has been adequately proven and its physico-chemical properties sufficiently described.

The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Nepipe Junior/Nepipe, 150 micrograms and 300 micrograms, solution for injection in pre-filled pen is formulated using excipients described in the current Ph Eur.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as the sensitivity for degradation by oxidation. The product contains a 10 % overage of adrenaline.

The manufacturing process has been well described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.
The tests in the drug product specification are considered appropriate to control the quality of the finished product in relation to its intended purpose. The analytical methods have been described and validated.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored not above 25°C.

III. NON-CLINICAL ASPECTS

This is a well established use application which is solely based on bibliographic data. Adrenaline/epinephrine has been studied extensively in various preclinical models and there is a long clinical experience with the substance. No new non-clinical data have been submitted and none are required.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

This is a well established use application which is solely based on bibliographic data. Limited pharmacokinetic information has been submitted. However, since epinephrine is to be administered as a single dose (maximum of two doses) intramuscularly, the limited pharmacokinetic information submitted is acceptable.

IV.2 Pharmacodynamics

The mechanism of action of epinephrine is considered well documented and established. Its effects include facilitation of venous return by α-adrenergic venoconstriction, β1-mediated positive inotropic, chronotropic, effects on the heart and β2-mediated bronchodilation. In mast cells and basophils β-adrenergic stimulation inhibits further inflammatory mediator release. The beneficial effect of epinephrine in the treatment of anaphylaxis is based on bronchodilator action and cardiovascular effects against the main symptoms in anaphylaxis: spasms of the bronchial muscles and drop in blood pressure.

Most of the clinically relevant undesirable pharmacodynamic effects occur when epinephrine is given in overdose or intravenously. The secondary vascular pharmacodynamic effects include increased renal vascular resistance and reduced renal blood flow, raises in arterial and venous pulmonary pressures and elevations in the concentrations of glucose, lactate, free fatty acids in blood, and decreases K+ in plasma. The metabolic effects are transient and of short duration. These effects do no are not considered to contraindicate its use in an acute life-threatening anaphylactic reactions.

There are several known pharmacodynamic interactions with epinephrine. However, in the setting of acute anaphylactic reaction with life-threatening features, initial treatment with epinephrine is of great importance and the concomitant individual medications may be considered while monitoring the response.

IV.3 Clinical efficacy

Clinical dose-finding studies on the use of epinephrine in the treatment of anaphylaxis have been performed neither in adults nor in children. The proposed dosing 0.3 mg adrenaline for intramuscular use in adults is considered well established. For children, the suggested posology is 0.15 mg adrenaline for intramuscular use depending upon the body weight of the

patient (0.01 mg/kg body weight) The proposed SmPC specifies also that the prescribing physician has the option of prescribing more or less than these amounts based on careful assessment of each individual patient and that the physician should consider using other forms of injectable adrenaline if lower doses are felt to be necessary for small children. This wording is endorsed.

There are no data available obtained from placebo-controlled or active comparator-controlled comparative clinical trials. In a study by Phillips et al. 29 serious anaphylactic reactions were treated immediately with 0.2 mg i.m. epinephrine doses. All who received early intervention with epinephrine responded but 9 patients were treated with more than 1 dose of epinephrine because of persistent symptoms. The proposed SmPC states that in the absence of clinical improvement or if deterioration occurs after the initial treatment, a second injection may be necessary. The prompt i.m. use of epinephrine as first line treatment of anaphylaxis is endorsed in well established clinical guidelines since >10 years in Europe. The data provided support the use of adrenaline in the treatment of anaphylaxis, irrespective of the trigger causing the reaction.

IV.4 Clinical safety

The literature search performed by the Applicant and the general approach to clinical safety is considered appropriate.

Side effects associated with adrenaline's alpha and beta receptor activity may include symptoms such as tachycardia and hypertension as well as undesirable effects on the central nervous system. Usual side effects are hyperhidrosis, nausea, vomiting, headache, dizziness, asthenia, tremor and anxiety. Cardiac arrhythmia may follow administration of adrenaline. Due to the potent local vasoconstrictor effect of epinephrine, accidental injection into digits in hands or feet may result in peripheral ischaemia requiring treatment. In rare cases stress cardiomyopathy has been seen in patients treated with adrenaline. In the clinical setting of acute anaphylaxis, it is not always possible to distinguish the anaphylaxis symptoms and possible adverse events of the treatment.

Obese patients might be possibly prone to accidental s.c. epinephrine administration with the currently established standard needle length of auto-injectors. A caution regarding the use of Nepipe Junior/Nepipe in patients with thick sub-cutaneous fat layer (see pharmacokinetic section) has been included in the SmPC.
The Applicant has comprehensively summarized the metabolic effects of epinephrine on laboratory findings. The Applicant´s conclusion: “Modest alterations of blood glucose or serum potassium levels following a single epinephrine self-administration of recommended doses are of minor clinical importance in this acute setting and symptomatic treatment may be considered after management of the acute emergency“ is endorsed.

Patients with hypertension, hyperthyreoidism, elderly patients with pre-existing cardiovascular disease, established coronary artery disease, diabetes or Parkinson´s diseaseare particularly susceptible to unfavourable effects. A statement in 4.4 concerning Parkinson´s disease has been added.

Caution is indicated in patients receiving drugs that may sensitise the heart to arrhythmias, including digitalis and quinidine. The effects of adrenaline may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors (MAO-inhibitors). Adrenaline inhibits the secretion of insulin.

The incidence of accidental injections, spontaneous activation and failures to activate per sold units is very low. The number of doses actually given is probably considerably lower than sold units, thus the incidence per given dose would be higher. However, it is acknowledged that it is not possible to provide a reliable estimate of doses actually given. Considering the high mortality of the untreated condition and the low reporting of serious outcomes such as death in relation to treatment with EpiPen this is acceptable, but device failures and handling errors remain a safety concern that should be continuously monitored.

V. BENEFIT/RISK ASSESSMENT, CONCLUSION, AND RECOMMENDATION

V.1 Benefit/Risk Assessment

Beneficial effects
Anaphylaxis is a severe, life-threatening, generalised/systemic hypersensitivity reaction that is rapid in onset and may cause death. Epinephrine is commonly acknowledged as the first line and single most important agent in the treatment of anaphylaxis.

Uncertainty in the knowledge about the beneficial effects
There are no data available obtained from placebo-controlled or active comparator-controlled comparative clinical trial due to ethically and medically reasonable constraints.

Unfavourable effects
Usual side effects are tachycardia and hypertension, hyperhidrosis, nausea, vomiting, headache, dizziness, asthenia, tremor and anxiety. Cardiac arrhythmia may follow administration of adrenaline.
Accidental injection into digits in hands or feet may result in peripheral ischaemia requiring treatment. In rare cases stress cardiomyopathy has been seen.

Uncertainty in the knowledge about the unfavourable effects
Post marketing experience has identified technical problems and handling errors in the use of epinephrine auto-injectors. The incidence of accidental injections, spontaneous activation and failures to activate per sold units is very low but the incidence per number of doses actually given is unknown.

Importance of favourable and unfavourable effects
There is a wide medical experience that the intramuscular epinephrine has a beneficial effect on possibly life-threatening anaphylaxis reactions and that is documented in well established guidelines. Intramuscular epinephrine is generally well tolerated but extreme caution is required in patients with cardiac disease. However, in cases life-threatening anaphylaxis, it is not possible to wave epinephrine administration in any patients

V.2 Conclusion on benefit-risk balance

The benefit risk balance is considered positive.

V.3 Recommendation

Nepipe Junior and Nepipe, 150 micrograms and 300 micrograms, solution for injection in pre-filled pen, is recommended for approval.

User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Epipen SE/H/137/01-02/R/02. The bridging report submitted by the applicant has been found acceptable.

VI. APPROVAL

The Decentralised procedure for Nepipe Junior and Nepipe, 150 micrograms and 300 micrograms, solution for injection in pre-filled pen, was successfully finalised on 2013-07-24.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval / non approval	Assessment report attached
Please see separate report attached at the end of this PAR.	SE/H/xxxx/WS/249	Yes	2018-09-15	2019-05-29	Approval	Yes

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LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Scientific conclusions from SE/H/xxxx/WS/249

SE/H/1287/01-02
Nepipe/Nepipe jr
(adrenaline)

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Data presented as requested in procedure (SE/H/xxxx/WS/249)

As a result of the Article 31 referral procedure for adrenaline auto-injectors (AAI), EMEA/H/A-31/1398, each Marketing Authorisation Holder of adrenaline auto-injectors were obligated to perform a PK/PD study to understand the influence of different factors on distribution, exposure and activity of adrenaline when administered via their adrenaline auto-injector device.

With this variation application for EpiPen (Fastjekt in Germany), the MAH has submitted the results from one clinical trial evaluating PK and PD parameters of adrenaline; Study EPIN-1508 was a Pharmacokinetic/Pharmacodynamic (PK/PD) study to evaluate adrenaline (epinephrine) exposure following intramuscular (IM) administration of Fastjekt Auto-Injector (0.3 mg; Mylan) in adult volunteers with varying skin-to-muscle distance (STMD) in the thigh.

Study EPIN-15083
The clinical phase of the study was conducted with the primary objective to estimate the differences in PK/absorption between Fastjekt® Auto-Injector, 0.3 mg following a single IM injection given at the mid-anterolateral thigh and adrenaline, 0.3 mg/0.3 mL delivered by syringe.

This was an open-label, single-dose, randomized, four-period, crossover study to investigate the PK and PD of Fastjekt® Auto-Injector, 0.3 mg following administration of a single, 0.3 mg (1 x 0.3 mg/0.3 mL) IM injection at anterolateral aspect of the mid-thigh (standard injection site) and the anterolateral aspect of the distal thigh in subjects that qualify for receiving injection at that site. Additional treatments included a 0.3 mL adrenaline IM injection (0.3 mg) at the standard injection site delivered by syringe and a 0.3 mL placebo IM injection at the standard injection site delivered by syringe.
Subjects were stratified into three (3) groups by STMD which was further balanced by gender:

- Group 1 - Six (6) males and six (6) females with maximum compressed STMD < 15mm
- Group 2 - Six (6) males and six (6) females with maximum compressed STMD ≥ 15mm and ≤ 20mm
- Group 3 - Five (5) males and six (6) females with maximum compressed STMD > 20 mm

On each study day dosing was performed following an overnight fast of at least 10 hours. Fasting continued for four hours post dose when a standardized meal was served. Subjects were in the resting/supine position beginning 90 minutes prior to dosing and remained so until 3 hours after dosing, except for brief periods when subjects were permitted to use the restroom.
On study day 1, each subject received either a single IM injection of 0.3 mg of Fastjekt AII given at the mid anterolateral aspect of the thigh, a single IM injection of 0.3 mg of Suprarenin (adrenaline) delivered by syringe given at the mid anterolateral aspect of the thigh, or a 0.3 mL dose of placebo (0.9% isotonic saline) delivered by syringe given at the mid anterolateral aspect of the thigh. A fourth treatment, a single IM injection of 0.3 mg of Fastjekt AII given at the distal anterolateral aspect of the thigh was administered to subjects only from Groups 2 or 3 with a STBD ≥ 20 mm. Following a 24-hour washout period, subjects were dosed with the alternative treatment as per the randomization.
In each study period, blood samples were collected at 90, 60 and 30 minutes prior to dosing and the following times after dosing: 3, 6, 9, 12, 15, 20, 25, 30, 40, 50, 60, 90, 120, 180, 240 and 360 minutes.
The individualized needle length used for syringe injections was determined by the average of the three minimum compressed ultrasound measurements taken at the mid anterolateral thigh. The needle length was approximately 30% longer than the subject's mean STMD to assure that the injection reached the muscle.
Blood pressure and pulse rate was measured at 90, 60 and 30 minutes prior to each dosing (following each blood sample collection), then at the following times a after each dosing (following each blood sample collection if at a similar time point): 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, 180, 240 and 360 minutes.

Pharmacokinetic results

Mean concentration versus time profiles for adrenaline given as a single IM injection of Fastjekt Auto-Injector applied at the mid anterolateral aspect of the thigh (Treatment A) demonstrated an earlier and higher adrenaline exposure (Cpeak: 0.515 ng/mL; Tpeak: 23.37 min) compared with a single IM injection of Suprarenin (adrenaline) delivered by syringe given at the mid anterolateral aspect of the thigh (Treatment B) (Cpeak: 0.351 ng/mL; Tpeak: 42.94 min) . The IM injection of Fastjekt Auto-Injector given at the distal anterolateral aspect of the thigh (Treatment D) showed also an early adrenaline exposure (Cpeak: 0.408 ng/mL; Tpeak: 27.09 min); however, there was no advantage in adrenaline exposure compared with Treatment A (i.e. administration of the Fastjekt Auto-Injector given at the mid anterolateral aspect of the thigh). See Figure 1.

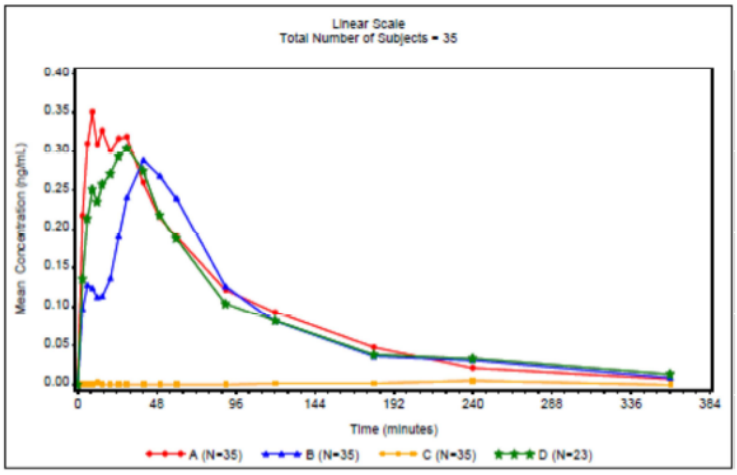
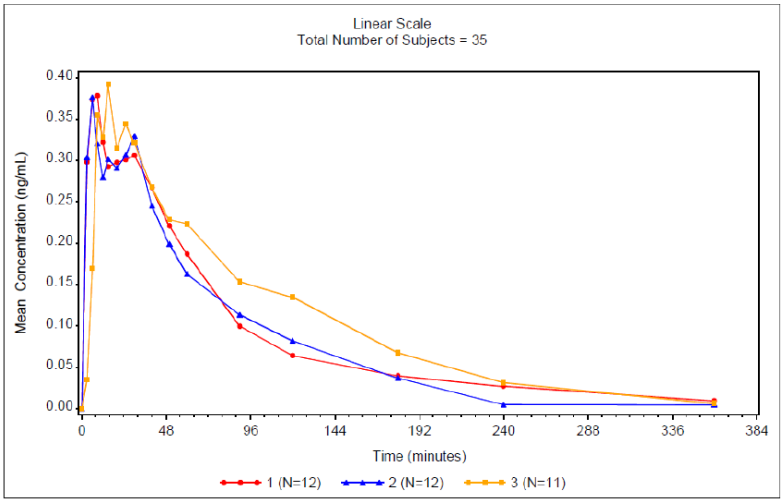


Figure 1. Mean adrenaline plasma concentrations (ng/mL) by treatment

It is concluded that the fastest absorption process was for Treatment A, based on all subjects. Treatment B, assessed in the same groups of subjects was 6-fold slower than Treatment A, indicating adrenaline absorption from a manual injection is considerably slower. Treatment D was only around 29% slower than treatment A; however, Treatment D included mid and upper STMD strata whereas Treatment A was based on all STMD strata for injection at the mid-anterolateral site. Treatment B can be concluded to be around 83% slower than Treatment A (6-fold).

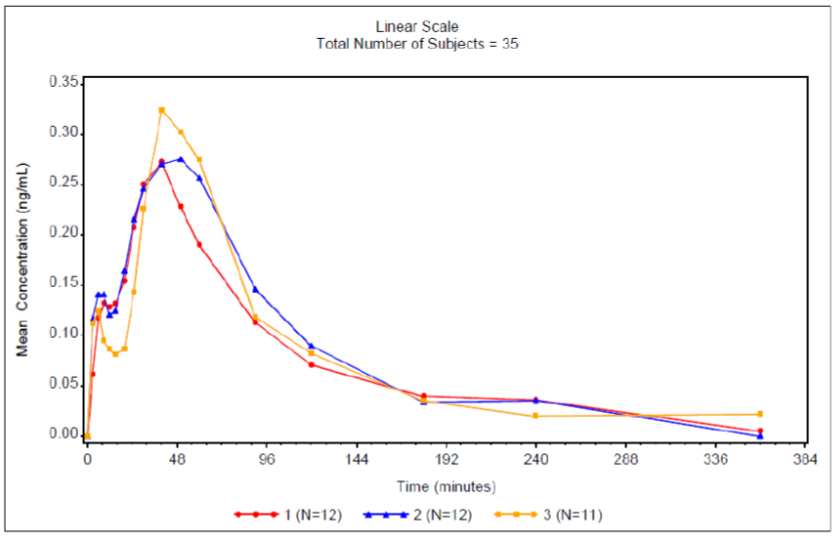
The mean concentration versus time profile for adrenaline by STMD group is illustrated graphically in Figure 2, Figure 3 and Figure 4.



Treatment A: Fastjekt® Auto-Injector (adrenaline), 0.3 mg/0.3 mL, mid anterolateral thigh injection

Group 1 - Six (6) males and six (6) females with compressed STMD < 15 mm
Group 2 - Six (6) males and six (6) females with compressed STMD ≥ 15 mm and ≤ 20 mm
Group 3 - Five (5) males and six (6) females with compressed STMD > 20 mm

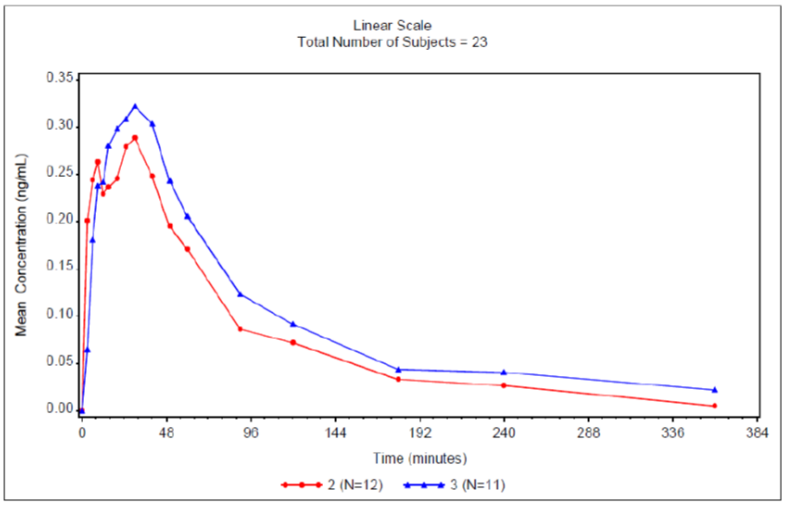
Figure 2. Adrenaline plasma concentration by STMD group-Treatment A



Treatment B: Suprarenin® ampoule (adrenaline), 0.3 mg/0.3 mL delivered by syringe, mid anterolateral thigh injection

Group 1 - Six (6) males and six (6) females with compressed STMD < 15 mm
Group 2 - Six (6) males and six (6) females with compressed STMD ≥ 15 mm and ≤ 20 mm
Group 3 - Five (5) males and six (6) females with compressed STMD > 20 mm

Figure 3. Adrenaline plasma concentrations by STMD group-Treatment B



Treatment D: Fastjekt® Auto-Injector (adrenaline), 0.3 mg/0.3 mL, distal anterolateral thigh injection

Group 2 - Six (6) males and six (6) females with compressed STMD ≥ 15 mm and ≤ 20 mm
Group 3 - Five (5) males and six (6) females with compressed STMD > 20 mm

Figure 4. Adrenaline plasma concentrations by STMD group- Treatment D

There is an indication of a slightly slower absorption in subjects with STMD >20 mm, compared to subject with lower STMD. Based on the evaluation of partial AUCs, the absorption of adrenaline from Epipen appears to be slower during the first six minutes in subjects with STMD >20 mm (cohort 3) compared to subjects with STMD <20 mm (cohort 1 and 2), although inter-individual variability was high.

Pharmacodynamic results

Heart rate and systolic blood pressure were among the parameters recorded. There were overall a considerable variation in results and there were no meaningful correlations between the adrenaline PK parameters (Cpeak, AUCt, AUCinf, Tpeak, Kel) and any of the PD measurements (pulse, systolic blood pressure, diastolic blood pressure) regardless of Treatment (auto-injector vs. syringe) as determined by r and τ values less 0.5.

Discussion
In general, adrenaline was rapidly absorbed following administration with both Fastjekt (EpiPen) and the comparator manual syringe. There was however an indication of a slightly slower absorption in subjects with high STMD (>20 mm) compared to subjects with lower STMD.
It was concluded that for the total study population as well as for the stratified populations based on STMD the adrenaline exposure via the Fastjekt® [Epipen] Auto-Injector given at the mid anterolateral aspect of the thigh, is adequate to treat emergency situations of anaphylaxis. Nevertheless, the partial AUCs during the initial 30 min were higher following injection with Epipen compared to manual intramuscular injection in all subgroups except in females with STMD>20mm for which concentrations were lower during the first 6-9 min for Epipen. One possible explanation for these results is the higher pressure obtained following injection with Epipen. It appears to be a potential risk of slower absorption in subjects with large STMD this is addressed in the SmPC which was amended as follows:

Section 4.4:
In patients with thick sub-cutaneous fat layer, there is a risk for adrenaline not reaching the muscle tissue resulting in a suboptimal effect ***(see section 5.2)***. ***A second injection with an additional Epipen may be needed (see section 4.2)***.

Overall conclusion, benefit/risk assessment and recommendation

The MAH has provided the results from a PK/PD study (EPIN-15083) in accordance with the Commission decision following the Art 31 referral procedure for adrenaline autoinjectors. In general, adrenaline was rapidly absorbed following administration with both Fastjekt (EpiPen) and the comparator manual syringe. There was however an indication of a slightly slower absorption in subjects with high STMD (>20 mm) compared to subjects with lower STMD. The risk of slower absorption in subjects with thick sub-cutaneous fat layer is already reflected in section 4.4 of the SmPC. Descriptive data has also been included in section 5.2. Some additional text is added to the warning in 4.4.

The product was approved since previously and the benefit/risk for the product remains unchanged.