CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Salmeterol/Fluticasone STADA 25 µg/50 µg/dose, Salmeterol/Fluticasone STADA 25 µg/125 µg/dose and Salmeterol/Fluticasone STADA 25 µg/250 µg/dose, pressurised inhalation, suspension STADA Arzneimittel AG, Germany

salmeterol (as salmeterol xinafoate)/fluticasone propionate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states during the evaluation process and provides a summary of the grounds for non approval of a marketing authorisation.
Some knowledge of medicines and diseases is expected as the language in this report may be difficult for laymen to understand.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The applicant has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1870/001-003/DC and NL/H/1871/001-003/DC
Registration number in the Netherlands: not applicable

26 August 2013

Pharmacotherapeutic group:	Adrenergics and other drugs for obstructive airway diseases
ATC code:	R03AK06
Route of administration:	inhalation
Therapeutic indication:	treatment of asthma where use of a combination product (LABA and ICS) is appropriate
Prescription status:	prescription only
Date of authorisation in NL:	Not applicable, non approval at day 210
Concerned Member States:	Decentralised procedure with DE
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered on Day 210 of the decentralised procedure that the application for Salmeterol/Fluticasone STADA 25 µg/50 µg/dose, 25 µg/125 µg/dose and 25 µg/250 µg/dose, pressurised inhalation, suspension in the proposed treatment of:

asthma where use of a combination product (LABA and ICS) is appropriate i.e., in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta-2-agonist (SABA), or in patients already adequately controlled on both ICS and LABA,

was not approvable, since "potential serious risks for public health" were identified. The details of these serious risks are provided in the report below. No marketing authorisation has been granted.

The products are orally inhaled combination products containing the active substances fluticasone propionate, an inhaled glucocorticosteroid with anti-inflammatory activity in the lungs and salmeterol xinafoate, a selective long-acting inhaled $ß_2$ adrenoceptor agonist. This combination of fluticasone propionate and salmeterol xinafoate is a well established combination of two known active substances and is formulated as a pressurised inhalation suspension with the hydrofluoroalkane (HFA) propellant, propellant HFA 134a (Norflurane), as a non-chlorofluorocarbon (CFC) propellant.

Fluticasone propionate is an inhaled glucocortosteroid with high local anti-inflammatory activity and a lower incidence of adverse effects than is seen with oral corticosteroids. Fluticasone propionate has been shown to reduce symptoms and exacerbations of asthma and to decrease airway reactivity to histamine and methacholine in patients with hyperreactive airways. Fluticasone propionate is a well established active substance and is recommended for use in the management of asthma in both adults and children.

Salmeterol xinafoate is a selective long-acting $ß_2$ adrenergic agonist and exerts a preferential effect on $ß_2$ adrenergic receptors on bronchial smooth muscle to produce relaxation and bronchodilatation. Salmeterol is used via the orally inhaled route in the management of patients with reversible airways obstruction. The inhalation of salmeterol produces bronchodilatation which lasts for 12 hours following a single dose. Salmeterol is particularly useful in patients with reversible airways obstruction who continue to experience symptoms despite treatment with an anti-inflammatory agent such as an inhaled corticosteroid. Guidelines for the management of reversible airways obstruction and particularly asthma recommend the addition of a long-acting $ß_2$ agonist to the treatment regimen in these patients.

This decentralised procedure concerns a hybrid "essential similarity/generic" application in accordance with article 10(3) of Directive 2001/83/EC. Essential similarity is claimed with the innovator product SERETIDE Evohaler® which was initially approved for the treatment of asthma in June 2000 in the UK (containing 25 µg of salmeterol (as salmeterol xinafoate) and 50, 125 or 250 µg of fluticasone propionate). A Dry Powder Inhaler form of this combination therapy was, however, first approved in Sweden on 7 September 1998. In the Netherlands, the reference products Seretide Inhalator CFK-vrij 25/50, 25/125 and 25/250 micrograms/dose (NL License RVG 25865-25867) have been registered by GlaxoSmithKline B.V. since 30 January 2001 through MRP UK/H/0392/001-003.

The Final version of CPMP/EWP/4151/00 Rev.1 '*Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents'* was adopted in January 2009 and took effect in August 2009. This requires that any abridged application must substantiate therapeutic equivalence to a marketed reference product.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in

the public domain. Authorisations for hybrid products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic/ pharmacodynamic profile of the product is similar to the pharmacokinetic/pharmacodynamic profile of the reference product. The applicant has submitted a comprehensive battery of comparative *in vitro* testing and 5 clinical studies to demonstrate equivalent efficacy and safety of the test product versus the reference product.

The potential serious risks to public health which preclude a recommendation for marketing authorisation, pertain both to quality and to clinical deficiencies.
The potential serious risk to public health from a quality point of view is that equivalence of the test and reference product has not been demonstrated when the products are used with a spacer device using clinically relevant manoeuvres.
With regard to clinical aspects, therapeutic equivalence is not proven with respect to efficacy and safety.

The application is made for use in adults, adolescents 12 years of age and older and children 4 years of age and older. The results of the clinical paediatric study NEO004 were not sufficient to prove therapeutic equivalence. Clinical development to support the use of these products in children and adolescents is required with demonstration of therapeutic equivalence in respect of both efficacy and safety.

No scientific advice has been given to the MAH with respect to these products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substances
Both salmeterol and fluticasone are established active substances described in the European Pharmacopoeia (Ph.Eur.*). Salmeterol xinafoate is a white or almost white powder which is practically insoluble in water, soluble in methanol and slightly soluble in anhydrous ethanol.
Fluticasone propionate is a white or almost white powder which is practically insoluble in water, sparingly soluble in methylene chloride and slightly soluble in alcohol.

The CEP procedure is used for both active substances. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substances
In addition to the Ph. Eur. and additional CEP requirements, there are other in-house specifications for both drug substances. These requirements have been justified. Batch analysis results are provided for 3 batches of both substances with results for all Ph. Eur. test parameters and in-house test parameters.

Stability of drug substances

For salmeterol, all results on 3 stability batches meet the set requirements. Based on the provided data, the claimed re-test period of 4 years without specific storage temperature can be accepted.
For fluticasone propionate stability data have been provided on three batches stored for 5 years at long-term and 6 months at accelerated conditions. All results meet the set requirements. Based on these data, the claimed re-test period of 2 years is justified without any specific storage conditions.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Salmeterol/Fluticasone STADA contains 25 micrograms of salmeterol (as salmeterol xinafoate) and 50, 125 or 250 micrograms of fluticasone propionate (delivered from the valve). This is equivalent to 21 micrograms of salmeterol and 44, 110 or 220 micrograms of fluticasone propionate delivered from the actuator (delivered dose).
The canister contains a white to off-white suspension. The aluminum container is fitted with a suitable metering valve and a plastic actuator.

The excipients are: norflurane (HFA 134a), lecithin as surfactant and ethanol (anhydrous).

Pharmaceutical development
The amount of both active substances delivered per actuation is identical to the reference product and in line with the formulation table. The data presented for the 2 sec delay for the Volumatic spacer show that it is not equivalent with the reference product. No satisfactory justification was provided for this difference. The clinical relevance of this difference should be demonstrated. In this case the actual risk is that equivalence of the test and reference product has not been demonstrated when the products are used with a spacer device using clinically relevant manoeuvres. Herewith this potential serious risk to public health has not been resolved during the registration procedure.
Comparative particle size distribution (PSD) data based on Anderson Cascade Impactor (ACI) between test and reference product for the three strengths have been provided. The data presented show that pooled stages 1-2 and stages 6-7 are not of consistent trend and linearity to the other stages. The clinical relevance of these differences has not been discussed. Therefore, the *in vitro* testing did not demonstrate sufficient comparability between the test product and the test product versus the reference product.

Manufacturing process
The manufacturing process consists of 6 steps and includes mixing, filling, weight checking, quarantine, post quarantine checking and assembly. Given the defined critical steps, the in-process controls and controls employed on intermediate product are appropriate.
Sufficient validation data have been provided on the different strengths.

Control of excipients
Pharmacopoeial tests are laid down for ethanol and lecithin. These specifications are acceptable. Sufficient testing is performed on norflurane.

Quality control of drug product
In general adequate drug substance specifications are proposed for description, identification, assay, uniformity of delivered dose, mean delivered dose, aerodynamic fine particle dose by ACI, number of deliveries, average weight of metered dose, particulate matter (only at release), related substances and leak test (only at release). Adequate validation data are provided for assay, related substances, related substances for forced degradation and ethanol determination. Batch analysis results are provided for batches of varying scale, divided over the three strengths.

Stability of drug product
For all three strengths for at least 3 batches 6 months accelerated data and 24 months normal data (25°C/60% RH) are available. No significant changes were observed, in the batches on the storage

conditions tested. Water content was seen to increase steadily and significantly, in all tested batches in the accelerated & long term conditions. The product complied with the microbial contamination specification in all the stability conditions for all the batches tested. No significant differences were observed between the stability results from samples stored in upright and inverted orientations. The claimed shelf-life of 2 years if stored below 25°C can be accepted. An in-use study on the 50/25 and 250/25 mcg, using batches near to shelf life, has been performed, showing satisfactory results.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Seretide, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.
Two leachables originating from the packing material were found in the product. However, the theoretical maximum daily exposure to these leachables is so low that it is not expected to be of relevant risk.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of salmeterol or fluticasone released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

The applicant has submitted 5 clinical studies to demonstrate equivalent efficacy and safety of the test product versus the reference product. Two studies were pharmacokinetic (PK) studies investigating lung deposition study NEO 045 and systemic bioactivity of Fluticasone and Salmeterol in study NEO 053. The applicant considers these two studies the pivotal studies for this hybrid essential similarity application with SERETIDE Evohaler® as a reference product. An additional supportive safety study PRC/CRD/25/08 is included in the dossier.

Pharmacokinetics
Two pharmacokinetic studies were submitted to support therapeutic equivalence of fluticasone propionate/salmeterol STADA 50/25, 125/25 & 250/25 micrograms per actuation and reference product Seretide Evohaler. Study NEO 045 was adequately designed to evaluate pharmacokinetics of fluticasone and salmeterol of test and reference product as support of therapeutic equivalence with respect to lung deposition. In study NEO 053 the AeroChamber spacer was applied and PK was only determined up to 2 hours after inhalation, predose levels were detected in 12 subjects for fluticasone and for salmeterol C_{max} was not determined adequately as sometimes maximum plasma concentrations had been reached the first time point. Therefore, this study does not fully comply with the Guideline *CHMP/EWP/4151/00 Rev. 1 – 22 January 2009* as a PK study to support safety. Nevertheless, PK data to support safety for fluticasone can be obtained from study NEO 045 because the contribution of oral absorption to the systemic exposure is negligible because of the high first-pass metabolism. Thus, study NEO 045 can support both safety and efficacy aspects of the fluticasone component. C_{max} concentrations are important for safety aspects of salmeterol and C_{max} is determined accurately in study NEO045. Thus study NEO045 is considered the pivotal study for evaluation of lung deposition and systemic exposure of fluticasone and to evaluate lung deposition of salmeterol and rate of absorption for safety assessment for salmeterol. Statistically evaluable information regarding extent of absorption of salmeterol for evaluation of safety is missing.

Pharmacokinetic parameters of fluticasone and salmeterol following 4 inhalations of 50/25 µg; 125/25 µg; 250/25 µg fluticasone/ salmeterol with test (neolab) and reference Seretide Evohaler product (non-transformed values; geometric mean, t_{max} median, ratio of test relative to reference) N=30 study NEO 045

AUC_{0-t} (pg/ml/h)								
Dose FP/SM	Fluticasone*				Salmeterol			
	Neolab	Seretide	Mean ratio	90%CI	Neolab	Seretide	Mean ratio	90%CI
50/25	4.8	5.6	0.86	**0.76**-0.97	502	290	1.73	**1.53-1.96**
125/25	5.5	7.9	0.70	**0.62-0.79**	497	338	1.47	**1.30-1.46**
250/25	7.1	6.8	1.05	0.93-1.18	370	287	1.29	1.14-**1.46**
$AUC_{0-\infty}$ (pg/ml/h)								
	Fluticasone*				Salmeterol			
	Neolab	Seretide	Mean ratio	90%CI	Neolab	Seretide	Mean ratio	90%CI
50/25	6.53	7.1	0.92	0.81-1.03	609	400	1.52	**1.36-1.71**
125/25	7.12	8.9	0.80	**0.71**-0.90	602	447	1.35	1.20-**1.51**
250/25	8.41	7.5	1.12	1.00-**1.26**	501	396	1.27	1.13-**1.42**
C_{max} (pg/ml)								
	Fluticasone*				Salmeterol			
	Neolab	Seretide	Mean ratio	90%CI	Neolab	Seretide	Mean ratio	90%CI
50/25	1.53	1.12	1.37	1.23-**1.53**	731	349	2.10	**1.87-2.35**
125/25	0.72	1.08	0.67	**0.60-0.74**	692	420	1.65	**1.47-1.84**
250/25	0.77	0.85	0.91	0.81-1.01	491	344	1.43	**1.27-1.60**
t_{max} (h)								
	Fluticasone				Salmeterol			
	Neolab	Seretide	Median difference	90%CI	Neolab	Seretide	Median difference	90%CI
50/25	0.08	0.88	-0.67	**-0.84, -0.46**	0.08	0.08	0.00	-0.03,0.0
125/25	0.14	1.26	-0.70	**-1.05,-0.22**	0.08	0.08	0.00	-0.02,0.0
250/25	1.25	1.50	0.00	-0.27, 0.25	0.08	0.08	0.00	0.00,0.00

* For Fluticasone mean values have been dose normalised to 1 mg. Values outside the 90% acceptance range are depicted in bold.

The results of submitted PK study NEO 045 (see table above) demonstrate that the test product at all three strengths fluticasone propionate/salmeterol 50/25, 125/25 & 250/25 micrograms per actuation is not bioequivalent to Seretide Evohaler: at the highest strength, 250/25 micrograms per actuation, the test and reference product appear equivalent with regard to the fluticasone propionate component; however fluticasone exposure was lower for the test product with the two lower strengths where inferiority in respect of efficacy is possible. At all three strengths, salmeterol exposure was considerably higher for the test product and this is of concern in respect of safety. Although there are several shortcomings with the

design of study NEO053, the results of study NEO053 were qualitatively consistent with the results of study NEO 045: rate and extent of absorption of salmeterol were higher for the test product. The effects on heart rate and serum potassium were more pronounced for the test product compared to the reference product, although the difference was not always statistically significant. Thus, equivalence with respect to safety between salmeterol/fluticasone STADA and Seretide Evohaler has not been demonstrated.

Clinical efficacy

Two clinical efficacy studies, one performed in adults (CP0705) and one performed in children (NEO004) were submitted as supportive studies to the pharmacokinetic studies.

NEO-004 is a phase III, randomised, double-blind, double-dummy, parallel group study to compare the efficacy and tolerability of HFA-propelled combination fluticasone propionate 50 µg and salmeterol xinafoate 25 µg pMDI with separate canisters of HFA-propelled fluticasone propionate 50 µg pMDI ("Flixotide Evohaler") and CFC-propelled salmeterol xinafoate 25 µg pMDI ("Serevent") in paediatric patients with mild to moderate asthma.

CP/07/05 is a randomised, double-blind, double-dummy, parallel group, multicentre study to compare the efficacy and tolerability of HFA-propelled combination fluticasone propionate 125 µg and salmeterol xinafoate 25 µg pMDI with separate HFA-propelled fluticasone propionate 125 µg pMDI ("Flixotide Evohaler") and CFC-propelled salmeterol xinafoate 25 µg pMDI ("Serevent") in subjects with mild to moderate asthma.

In both studies the primary objective was defined as to determine the non-inferiority of the clinical effect of a combination fluticasone propionate plus salmeterol xinafoate pMDI with the two single-product pMDIs.

The clinical studies CP0705 and NEO004 were not designed properly to prove therapeutic equivalence between the test product and individual single products. Both studies were designed as non-inferiority studies. They lack assay sensitivity, since only one dose of one strength of the fixed-dose combination of the test product and similar doses of the individual canisters of the reference products were administered.
Therefore neither study demonstrates therapeutic equivalence. Determination of non-inferiority is not sufficient.
Moreover, in both studies the fixed-dose combination of the test product was compared to similar doses of the individual canisters of the fluticasone ("Flixotide Evohaler") and salmeterol ("Serevent") and not the current combination reference product, "Seretide Evohaler". According to Guideline on the requirements for clinical documentation for orally inhaled products (OIP) (CPMP/EWP/4151/00 Rev.1) the test product should be compared to the reference fixed dose product.
To determine therapeutic equivalence of a fixed combination product efficacy and safety of the combination of an ICS and a LABA might be investigated in one study in which outcome measures capable of assessing both active components in the combination separately are included, i.e separate variables in respect of efficacy will need to be defined, one for each component of the combination. Another possibility is to establish therapeutic equivalence through separate studies assessing equivalence of each separate active substance.
In the clinical studies only one clinical endpoint (change of mean morning PEF between baseline and week 11-12) was used measuring the effect of both components together. Both salmeterol and fluticasone influences PEF. Therefore the endpoint is considered insufficient for establishing therapeutic equivalence of each component of this fixed combination. Besides, in adults the Guideline on the requirements for clinical documentation for orally inhaled products (OIP)(CPMP/EWP/4151/00 Rev.1) requires to measure the efficacy of salmeterol following inhalation of a single dose through either measurement of bronchodilatation over at least 80% of the duration of action or bronchial challenge studies; the efficacy of the ICS component will be through the study of multiple dose inhalations over time – see sections 6.2.3.1 and 6.2.3.2, of the Guideline. For children also FEV1AUC is preferred although for preschool children this is not feasible.

In the paediatric study NEO-004 the patients were stratified into 3 groups to ensure even distribution of 4-6 year olds between the two treatment groups, and to ensure equivalent numbers of spacer-users/non spacer-users in each group.
Stratum A = Patients who are over 6 years old and do not use spacer
Stratum B = Patients who are over 6 years old and use spacer

Stratum C = Patients who are 4-6 years old and use spacer
However, the presented results are not stratified. A part of the children used a spacer while another part did not. The results of this study are composed of results with and without the use of a spacer. The use of a spacer influences deposition. Therefore equivalence in deposition has to be tested with and without spacers separately.Therefore neither therapeutic equivalence without use of a spacer nor therapeutic equivalence with use of a spacer can be determined.
Clinical development to support of the use of these products in children 4 years of age and older and adolescents 12 to 17 years of age is still required with demonstration of therapeutic equivalence.

Clinical safety
Beside the studies CP0705 and NEO004, another supportive safety study PRC/CRD/25/08, is included to compare the post first-dose effect and tolerance.
PRC/CRD/25/08 was a randomised, double blind, double dummy, two-period crossover study to compare the post first dose effects after inhalation of a single dose of fluticasone/salmeterol HFA combination pMDI Cipla with the reference fluticasone/salmeterol HFA combination pMDI (Seretide Evohaler) in patients with asthma. The value of this study is only supportive regarding post first dose effects and tolerance of the new product. There was no significant fall in FEV1 (≥ 15%) reported after the study drug administration in both the test and the reference group after 10 minutes after administration. There were no differences in post first dose symptoms of cough, wheeze or breathlessness reported by the subjects in both the treatment groups.

The findings in respect of safety of CP0705 and NEO004 were not sufficient to assess systemic safety. Systemic safety is to be assessed through a comparative systemic PK study or through the pharmacodynamic assessment of systemic effects of ICSs by the effect on the hypothalamic pituitary adrenocortical (HPA) axis. The preferred pharmacodynamic method of assessing the HPA axis is the repeated assessment of the change from baseline in 24-hour plasma cortisol as measured by AUC (as the primary variable) and C_{max}.
The submitted urinary analysis in study CP0705 is not sufficient due to the small number of patients.
Therapeutic equivalence in respect of safety is not proven.

Paediatric Development Plan
The Applicant requested Marketing Authorisations for use in adults, adolescents 12 years of age and older and children 4 years of age and older. The results of the clinical paediatric study NEO004 were not sufficient to prove therapeutic equivalence. Clinical development to support the use of these products in children and adolescents is required with demonstration of therapeutic equivalence in respect of both efficacy and safety.

Spacing device – AeroChamber Plus Device
Both the AeroChamber Plus spacing device and the Volumatic spacing device are recommended for use with the reference product Seretide, when used by children and by all patients who are unable to synchronise actuation of the pMDI with inspiration of breath. Therefore *in vitro* and *in vivo* data should be provided for the test product with the device to be used compared to the reference product with both the AeroChamber Plus spacing device and the Volumatic spacing device (see also III.1 Quality aspects). These data were not provided.

The overall clinical conclusion is that therapeutic equivalence is not proven with respect to efficacy and safety of these orally inhaled fixed-dose combination products each formulated in three strengths, Salmeterol/Fluticasone STADA 25/50, 25/125 & 25/250 micrograms CFC-Free Inhaler across the entire age range of intended use, adults, adolescents 12 years of age and older and children 4 years of age and older.

Risk management plan
As the application for these products was not approved, the evaluation of the risk management plan is no longer relevant.

Product information

SPC
As requested, the applicant updated the SPC and PL according to the texts for the reference product Seretide Evohaler UK/H/0392/001-003.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
According to the readability index (RI) a high percentage (99%) of the information requested in the questions was found and understood correctly. 297 out of 300 pieces of information were found and understood. In general the conclusions are clear, concise and clearly presented and they reflect the results of the test. Overall the test subjects were satisfied with the readability of the text. They were also satisfied with the clarity of the text, the graphical layout, and the font style and size. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The member states, on the basis of the data submitted, considered that Salmeterol/Fluticasone STADA 25 µg/50 µg/dose, 25 µg/125 µg/dose and 25 µg/250 µg/dose, pressurised inhalation have not demonstrated a satisfactory risk/benefit profile (see also discussion below). Therefore, the procedures NL/H/1870-1871/001-003/DC were finalised with a negative outcome on 18 January 2011, and no marketing authorisation was granted.

Two pivotal clinical studies were performed with the primary objective to determine the non-inferiority of the combination fluticasone propionate plus salmeterol xinafoate pMDI versus the two single-product pMDIs. Both studies lack assay sensitivity, since only one dose of one strength of the fixed-dose combination of the test product, and similar doses of the individual canisters of the reference products were administered. Therefore neither study demonstrates therapeutic equivalence. Moreover, in both studies the fixed-dose combination of the test product was not compared to the current combination reference product, “Seretide Evohaler” as described in the relevant Guideline for orally inhaled products (OIP) (CPMP/EWP/4151/00 Rev.1).

The Board followed the advice of the assessors. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that the product has not been demonstrated to be of therapeutic equivalence to the reference product Seretide Evohaler. Based on the currently available data no marketing authorisations could be granted.

List of abbreviations

ACI	Anderson Cascade Impactor
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
pMDI	pressurised Metered-Dose Inhaler
PSD	Particle Size Distribution
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached