CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Fluticasonpropionaat 50 A, nasal spray, suspension 50 micrograms/dose Apothecon B.V., the Netherlands

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.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

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 MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 103003

18 August 2010

Pharmacotherapeutic group:	decongestants and other nasal preparations for topical use, corticosteroids
ATC code:	R01AD08
Route of administration:	nasal
Therapeutic indication:	prophylaxis and treatment of allergic rhinitis and *rhinitis vasomotorica.*
Prescription status:	prescription only
Date of authorisation in NL:	29 June 2009
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 quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Fluticasonpropionaat 50 A, nasal spray, suspension 50 micrograms/dose from Apothecon B.V. The date of authorisation was on 29 June 2009 in the Netherlands.

The product is indicated for the prophylaxis and treatment of allergic rhinitis and *rhinitis vasomotorica.*
A comprehensive description of the indications and posology is given in the SPC.

Fluticasone propionate is a glucocorticosteroid and has potent anti-inflammatory activity but when used topically on the nasal mucosa has no detectable systemic activity. Fluticasone propionate causes little or no hypothalamic-pituitary-adrenal axis suppression following intranasal administration.
Following intranasal dosing of fluticasone propionate, (200mcg/day) no significant change in 24h serum cortisol AUC was found compared to placebo (ratio 1.01, 90%CI 0.9-1.14).

This national procedure concerns a so-called hybrid application claiming essential similarity with the innovator product Flixonase 50 micrograms/dose, aqueous nasal spray (NL License RVG 14424) which has been registered in the Netherlands by GlaxoSmithKline B.V. since 28 November 1990.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC.

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 generic 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. In accordance with the *Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products containing Known Constituents* (CPMP/EWP/239/95), a pharmacokinetic study is required for a suspension formulation to show bioequivalence in absorption of fluticasone between test and reference product, or a clinical study with sufficient assay sensitivity should demonstrate non-inferiority of test (FTP) to reference product. The MAH submitted the results of two clinical studies. Non-inferiority was sufficiently demonstrated. The current product can be used instead of its reference product.

No new pre-clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for a hybrid application.

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 this product type 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 substance
The active substance is fluticasone propionate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance a white to almost white powder, which is insoluble in water, sparingly soluble in methylene chloride and slightly soluble in alcohol. It was demonstrated that no polymorphism is to be expected.

The Active Substance Master File (ASMF) procedure is used for one supplier of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

The CEP procedure is used for the other supplier of the active substance. 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.

** 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.*

Manufacturing process
The manufacturing process consists of the turnover of flumethasone in seven steps into fluticasone propionate. Detailed information on the manufacture has been provided for the DMF-holder. For the other manufacturer, information on the manufacturing process is covered by the CEP.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. The specifications are acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided from seven pilot-scale batches and three production-scale batches.

Stability of drug substance
Fort the first supplier, the presented stability results were obtained by testing three batches that are produced following the smaller scaled "old" manufacturing procedure, and two batches that are produced in accordance with the current manufacturing procedure.
The three batches that were produced following the smaller scaled "old" manufacturing procedure, were stored at 25°C/60% RH (48 months) and at 40°C/75% RH (6 months).
The two batches that were produced in accordance with the current manufacturing procedure, were stored at 25°C/60% RH for 24 months and 12 months respectively. The results show that none of the tested parameters is susceptible to change during the tested period. The active substance is stable under both,

long term and accelerated conditions. The proposed shelf-life of five years with no specific storage conditions could be granted.
For the active substance obtained from the CEP holder a retest period of 3 years is applicable. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Medicinal Product

Composition
Fluticasonpropionaat 50 A is a white aqueous suspension (pH 5.0-7.0) containing 50µg of fluticasone propionate per metered dose.

The nasal spray suspension is packed in amber type I glass bottles fitted with a white, metering atomising pump, a white nasal adapter and a clear dust cap placed in a cardboard outer box. The bottle sizes are 6 ml and 15 ml.

The excipients are: glucose (anhydrous), microcrystalline cellulose (E460 i) and sodium carboxymethyl cellulose (E466) (Avicel RC591), phenylethyl alcohol (0.25% g/g/), benzalkonium chloride (0.02% g/g), polysorbate 80 (E433), purified water.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The composition of the drug product is based on the innovator's product. From a chemical pharmaceutical point of view, essential similarity can be demonstrated by comparing the drug product with a UK reference product. The following physical, chemical parameters were compared: droplet size distribution, uniformity of the delivered dose and comparative batch analyses.
The Dutch marketed product is registered through a national procedure; therefore similarity between the UK reference product and the Dutch marketed product has been demonstrated by comparison of description, identification, pH, assay, impurities, benzalkonium assay, phenylethyl assay, uniformity of mass and mean delivered dose. Furthermore, particle size distribution in the reference product and the proposed product has been compared and considered to be comparable.

Manufacturing process
The product is manufactured at two different manufacturing sites in a straight forward manufacturing method, which consists of the sequential addition and either dispersion or dissolution of solid materials in water. Since the drug product consists of a suspension, it is considered to be a non-standard manufacturing process. Process validation data on the product has been presented for four full-scale batches from one site, and for three full-scale batches from the other site.

Container closure system
The product is packaged in amber, type 1 glass bottles fitted with a white, metering, atomising pump, white nasal adapter a clear dust cap, contained in a carton. Three pack sizes of 60, 120 or 150 sprays are proposed. There are two bottle sizes, 6 and 15 ml. The 6 ml bottle contains 60 sprays and the 15 ml bottle either 120 or 150 sprays each delivering 50µg of fluticasone propionate in 100 mg (=100µl) of formulation through the nasal adapter.

Control of excipients
The excipients comply with the Ph.Eur. with the exception of Dispersible cellulose , which complies with the British Pharmacopoeia (BP) and phenylethyl alcohol which complies with the Pharmacopoeia of the United States (USP). These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification and includes tests for appearance, identification, pH, assay, impurities, uniformity of delivered dose, uniformity of mass (pump delivery), foreign particulates/content, net contents, microbial limits, mean delivered dose, number of actuations per container.

The analytical methods used by both production sites have been adequately described and validated per site. Batch analytical data from the proposed production sites have been provided on three full-scale batches from one site, and for and four full-scale batches from the other, demonstrating compliance with the release specification.

Stability of drug product
For one manufacturer, stability data on the product have been provided on three pilot-scale batches stored in upright and horizontal position at 25°C/60% RH (24 months) and 40°C/75% RH and nine full-scaled batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months).
Three production-scale batches of drug product from the other manufacturing site were stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). .
The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. No difference was observed between the upright and horizontal stored bathes. Also, no significant trends or changes were seen. No photostability study was undertaken but since the product is contained in an amber glass bottle and the reference product does not have any special warning regarding light exposure, this is acceptable.
Based on the results of stability testing, a shelf life of 2 years could be granted with the applicable storage condition *Store below 25°C*.

An in-use storage time of three months was initially claimed. However, given the fact that no change in stability occurs after first opening of the container and the fact that the reference product has no in-use shelf-life, the in-use storage time is the same as shelf life.

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 active substance has been available on the Dutch market since 1990. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

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 fluticasone propionate 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

Fluticasone propionate is a well-known active substance with established efficacy and tolerability.

In support of this hybrid application, the MAH provided the results of two studies. The MAH provided sufficient information to demonstrate that the product to be marketed is identical to the product used in the clinical studies .The results of these studies are discussed below.

Pharmacokinetics
The MAH submitted a pharmacokinetic study comparing the biovailability of their fluticasone aqueous nasal spray (FTP) formulation with that of the innovator product. The study was undertaken according to the principles of GCP.

Design

This was a randomised, open-label, three-way crossover study comparing the pharmacokinetic and safety profile of the 50 micrograms/dose formulation with that of the originator intranasal fluticasone products (Flonase, GSK Ltd (US product) and Flixonase, GSK Ltd (UK product)). A total of 80 subjects aged 18-54 years were screened and 60 were randomised, seven patients withdrew from the study for personal reasons. As only a minimal amount of fluticasone is absorbed by the nasal route a dose of 800 mcg was chosen in order to provide measurable plasma levels in the picog/ml range.

Following screening subjects received a single 800 mcg dose (8 sprays of 50 mcg per nostril) of one of the three study treatment on three separate occasions 2-7 days apart. Plasma samples were taken pre-dose and at 10, 20, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 18 and 24 hours post dose on each occasion.

Analytical Methods
0.5 ml plasma samples were analysed for fluticasone using liquid chromatography mass spectrometry (LC-MS/MS). The lower limit of quantification was 3 pg/ml. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Results that are directly relevant to the assessment of the product in Europe, i.e. the comparison of the tluticasone propionate test product (FTP) versus the European reference product (Flixonase, GSK Limited, UK), are presented.

	t_{max} (hours) (SD)	**$t_{1/2}$ (hours) (SD)**	**Ratio AUC_{0-t}(pg/ml.hr) (90% CI)**	**Ratio C_{max} (pg/ml) (90% CI)**
Test	0.96 (0.11)	15.97 (2.85)	-	-
Reference	0.94 (0.11)	20.40 (2.85)	0.95 (0.80-1.06)	0.95 (0.88-1.03)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
C_{max}	maximum plasma concentration			
t_{max}	time for maximum concentration			
$t_{1/2}$	half-life			

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters of fluticasone, it can be concluded that systemic exposure to fluticasone is similar for both formulations.

Clinical Efficacy
A single therapeutic equivalence study was conducted.

Design
This was a multicentre, randomised, double-blind, double-dummy, parallel-group study undertaken in patients aged 12 years or older designed to investigate the safety and efficacy of FTP compared to Flonase and Flixonase and placebo administered for 13 to 15 days. The study was conducted at six study sites located in central Texas during the mountain cedar (*Juniperus ashei*) pollen season. There were four study visits at Screening, Day 1, Day 8 and Day 15. There was a 3- to 21-day run in period between the Screening visit and Day 1. Patients were randomly assigned in a 2:1 ratio (active to placebo) and study drug was administered for 13 to 15 days.

The primary objective of the study was to establish bioequivalence of the investigational product, FTP, with Flixonase and Flonase. In addition, the efficacy of each active formulation versus placebo was to be demonstrated.

There was a 4-week placebo run-in period. The ITT population has 514 patients in it - 74 on placebo, 146 on FTP, 146 on Flonase and 148 on Flixonase.

Efficacy Measurement
Primary Endpoint:
The mean patient rated total nasal symptom score (TNSS) over the entire treatment period (using AM and PM individual nasal symptom scores averaged from diary cards). The TNSS (reflective score was comprised of the four symptoms most prevalent in seasonal allergic rhinitis: rhinorrheas, nasal stuffiness/congestion, nasal itching, and sneezing.

Results
The primary endpoint was the difference in mean $\log_{10}$ (TNSS+1) between the FTP and both the Flonase and Flixonase groups. The primary analysis of this endpoint was an analysis of covariance with fixed effects for treatment group and investigator, and with baseline-combined AM and PM TNSS as a covariate. Overall, the statistical analysis is appropriate.

The results on the original scale with 95% confidence intervals for the primary endpoint for the per protocol population are summarised in the table below. Note the results for the ITT population are very similar.

Equivalence Assessment	**Estimate[1]**	**95% Confidence Interval[2]**
($\log_{10}$ Scale) Mean difference between FTP and combined Flonase and Flixonase groups	0.0074	(-0.0324,0.0472)
(Absolute Scale) Mean Ratio of FTP to combined Flonase and Flixonase groups	1.02	(0.93,1.11)

[1] The Analysis is based on a linear two-way analysis of covariance with fixed effects for treatment group and investigator, and with baseline combined AM and PM TNSS as a covariate.
[2] Equivalence to FTP to a reference product was concluded if the 95% CI for the difference in mean $\log_{10}$ (TNSS+1) was contained within the interval of (-0.0969,0.0969) (i.e. (0.8,1.25) on the ratio scale).

For comparison the results for the original TNSS scale, average change over the treatment period and average percentage change from baseline on this scale are shown in the tables below (per protocol analysis). Note the results for the ITT analyses were very similar.

Patient rated combined AM and PM TNSS score average over the treatment period (Per protocol)

	Placebo N=69	**FTP N=142**	**Flixonase N=143**	**FTP vs Flixonase**
Mean (SD)	6.5 (2.7)	4.9 (2.3)	4.9 (2.5)	-
LS Mean (SE)	6.4 (0.27)	4.9 (0.18)	4.9 (0.18)	-
95% CI	5.9-6.9	4.5-5.3	4.5-5.3	-
Median	7.0	4.7	4.7	-
Min, Max	1.2, 11.7	0.5, 10.6	0.4, 12.0	-
LSM Difference (SE)	-	-	-	0.0089 (0.261)
95% CI	-	-	-	-0.5.05 – 0.522
P value	-	-	-	0.9729

Average change over the treatment period in patient rated combined AM and PM TNSS (Per protocol)

	Placebo N=69	**FTP N=142**	**Flonase N=144**	**Flixonase N=143**	**Difference FTP v Flixonase**
Mean (SD)	-1.8 (2.46)	-3.1 (2.63)	-2.9 (2.36)	-3.1 (2.48)	
95% CI	-2.4, -1.2	-3.5, -2.7	-3,3, -2.5	-3.5, -2.7	-0.58, 0.58 (p =0.999)
Median	-1.6	-2.9	-2.7	-3.1	
Min, Max	-9.7, 3.2	-11.5, 3.0	-9.7, 3.3	-9.9, 2.7	

Average percentage change from baseline in patient rated combine AM and PM TNSS (Per protocol)

	Placebo N=69	FTP N=142	Flixonase N=143
Mean (SD)	-19.6 (29.55)	-35.7 (30.49)	-37.8 (28.93)
95% CI	-26.6, -12.7	-40.6, -30.9	-42.6, -32.9
Median	-20.5	-37.0	-39.8
Min, Max	-82.7, 60.4	-95.5, 70.1	-93.2, 55.4

The results from this study show very similar efficacy for all three active products. The 95% confidence interval for the difference between FTP and Flixonase on the change from baseline of the TNSS scale has a lower limit of about -0.5 unit. The MAH justified the clinical insignificance of differences that would correspond to differences of 0.8 or 1.25 on the ratio scale. The MAH stated that these limits corresponds to a ±20% difference between treatments and that it corresponds to a minimal measurable clinical difference on the TNSS scale of 1 unit. The MAH also discussed other studies in this area that have used similar equivalence limits. The observed limits of the confidence interval are about ±0.5 unit. As placebo controlled data have been submitted the superior of FTP to placebo is not in question. The appropriate size of equivalence margin then becomes a clinical decision of what constitutes a clinically insignificance difference between treatments. Provided it is accepted that the minimum detectable difference on the TNSS scale is 1 unit then these data provide good evidence of therapeutic equivalence as the data suggest that the difference between FTP and Flixonase is unlikely to be more than 0.5 unit on the TNSS scale.

Conclusions

- The difference between the average TNSS scores for FTP and Flixonase are both clinically and statistically insignificant.
- The difference between the average change from baseline TNSS scores for FTP and Flixonase are both clinically and statistically insignificant.
- FTP and Flixonase may be regarded to be therapeutically equivalent.

Clinical safety

Introduction

A total of 684 patients were randomised into the two clinical studies. Of these, 74 received placebo, 204 received FTP, 206 received Flonase and 207 received Flixonase.

Adverse Events

The incidence of adverse events was similar across the treatment groups. Those adverse events considered treatment-related included nasal burning, headache and epistaxis. There was not judged to be any clinically significant difference between the active treatment groups.
There were no serious adverse events or deaths reported.

Laboratory Data

No clinically relevant differences were seen in routine laboratory parameters. There was a slight increase in mean serum cortisol values over the course of the study in all treatment groups. Four patients were found to have a low serum cortisol level at Day 15 (one on placebo, two on FTP and one on Flixonase), but these were not considered clinically significant.
The safety of intra nasal fluticasone preparations is reviewed in the clinical overview.

Conclusions

- The safety of FTP is similar to that of Flixonase.
- It is well recognised that minor nose bleeds occur with steroid nasal sprays, likewise other adverse event seen in the clinical studies were consistent with the known adverse effects of nasal fluticasone preparations.

Overall benefit-risk assessment

The clinical programme provides adequate data of the efficacy and safety of FTP. It may be concluded that FTP has been shown to be therapeutically equivalent to the innovator Flixonase and it would therefore be expected that FTP would have the same benefit and risks as the innovator product when used at the same dose, with the same delivery system and for the same indication area.

Risk management plan

Fluticasone was first approved in 1990, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of fluticasone can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The proposed SPC is identical to that of the Dutch innovator product, Flixonase, except section 4.8, which is in accordance with the current SCP Guideline.

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 two rounds with 10 participants each. Fifteen questions were prepared to test for the understandability and the applicability of important information in the PIL. The findability was tested in all the fifteen questions.

The Fluticasone readability test has demonstrated that several aspects of the PIL could be improved. In line with comments of the volunteers the PIL was adapted. Since the changes were relatively minor, a re-test of the adapted PIL was not considered necessary. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Fluticasonpropionaat 50 A, nasal spray, suspension 50 micrograms/dose has a proven chemical-pharmaceutical quality and is a hybrid form of Flixonase 50 micrograms/dose, aqueous nasal spray. Flixonase is a well-known medicinal product with an established favourable efficacy and safety profile.

Non-inferiority to the reference product was sufficiently demonstrated in two clinical studies. The current product can be used instead of its reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Fluticasonpropionaat 50 A, nasal spray, suspension 50 micrograms/dose was authorised in the Netherlands on 29 June 2009.

There were no post-approval commitments made during the procedure.

List of abbreviations

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
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
MA transfer and consequential change in product name.	--	MA transfer	22-7-2009	12-8-2009	Approval	N
Change to batch release arrangements and quality control testing of the finished product; replacement or addition of a site where batch control/testing takes place.	--	IA	14-12-2009	31-1-2010	Approval	N
Change in test procedure for the finished product; other changes to a test procedure (including replacement or addition).	--	IB	10-3-2010	29-3-2010	Approval	N
Change in the specification parameters and/or limits of the immediate packaging of the finished product; addition or replacement of a specification parameter as a result of a safety or quality issue.	--	IB	10-3-2010	29-3-2010	Approval	N
Change in shape or dimensions of the container or closure of non-sterile medicinal product.	--	IA	10-3-2010	14-5-2010	Approval	N
Replacement or addition of a supplier of packaging components or devices.	--	IA	10-3-2010	14-5-2010	Approval	N
Change in immediate packaging of the finished product; semi-solid and non-sterile liquid pharmaceutical forms.	--	IB	10-3-2010	29-3-2010	Approval	N
Change in batch size (including batch size ranges) of the finished product.	--	IA	6-4-2010	6-6-2010	Approval	N