COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tavulus 18 microgram, inhalation powder in hard capsules

(tiotropium bromide)

NL/H/5048/001/DC

Date: 12 October 2021

This module reflects the scientific discussion for the approval of Tavulus. The procedure was finalised at 6 April 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
COPD	Chronic Obstructive Pulmonary Disease
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FPD	Fine Particle Dose
HV	Healthy Volunteer
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
NGI	Next Generation Impactor
NSR	Non-Significant Risk
Ph.Eur.	European Pharmacopoeia
PIF	Peak Inspiratory Flow
PIFR	Peak Inspiratory Flow Rate
PK	Pharmacokinetic
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tavulus 18 microgram, inhalation powder in hard capsules from Glenmark Pharmaceuticals s.r.o.

The product is indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Spiriva 18 microgram inhalation powder in hard capsules (NL License Number 26191) which has been registered in the Netherlands with procedure number NL/H/0299/001/MR by Boehringer Ingelheim International GmbH since 2001 (original product).

The concerned member states (CMS) involved in this procedure were France and Spain.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC. This application concerns a hybrid application as Tavulus utilises a different type of inhalation device than the reference product Spiriva.

II. QUALITY ASPECTS

II.1 Introduction

Tavulus is a transparent colourless hard capsule containing a small amount of white inhalation powder with 'T10' printed on the capsule.

Tavulus contains as active substance 21.7 microgram tiotropium bromide amorphous equivalent to 18 microgram tiotropium. The delivered dose (the dose that leaves the mouthpiece of the inhaler) is 10 microgram tiotropium.

The capsules are packed in aluminium/ PVC/aluminium unit-dose blisters. The blisters are supplied in a carton box with a dry powder inhaler device.

The only excipient present in Tavulus is lactose monohydrate (which may contain small amounts of milk proteins).

II.2 Drug Substance

The drug substance tiotropium bromide monohydrate is described in the European Pharmacopoeia (Ph. Eur.) However, in this product tiotropium bromide amorphous is used. Tiotropium bromide is a brownish to off-white powder. The active substance in the applied product comes as amorphous and in the anhydrous form, compared to the crystalline and monohydrate form of the reference product. Stereochemistry is not a concern as it is a non-chiral molecule, with four stereogenic and one anomeric carbon atoms.

The Active Substance Master File (ASMF) procedure is used for 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.

Manufacturing process

The manufacture starts with hydrolyses that yields intermediate compound one in two steps. The second arm yields intermediate compound two after a conversion step. Intermediate compounds one and two are coupled together followed by crystallisation and purification processes to yield the active substance described as a four step process. The final stages are four crystallisation steps with different solvent combinations and micronisation to yield the required particle size of the final active substance. There is no use of class one solvents or heavy metal catalyses. The process has been adequately described.

Quality control of drug substance

The active substance specification is provided in the Active Substance Master File. The specification is 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 for three pilot scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three pilot scale batches stored at 2-8°C (24 months) and (25°C/60%RH (six months). The batches were stored in glass or HDPE bottles in sealed aluminium bags (as intended for marketing) in accordance with applicable European guidelines demonstrating the stability of the active substance for two years. Additional testing at 40°C/75%RH was performed to cover transport and temperature excursions, for up to two weeks. The stability data support two years at long term storage condition (2-8°C). Based on the data submitted, a retest period could be granted of 24 months when stored at long term storage conditions (2 - 8°C).

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The choice of excipient is justified and their functions explained. The development is based on the reference product Spiriva and has followed the European Medicines Agencies (EMA)´s guideline on inhalation products (EMA/CHMP/QWP/4913/2005). Key and critical features of the development are characterising the particle size distribution of the drug substance and relevant controls thereof. Furthermore, studies such as specific surface area and rugosity have been performed. There is only one excipient, lactose monohydrate, and numerous studies were performed to select the most suitable grade, to demonstrate equivalence with the reference product. Similarly, various capsules were tested to select the most suitable to deliver the right dose in combination with the powder. For development purposes and to support therapeutic equivalence, results of four pharmacokinetic (PK) studies have been submitted. The test- and reference products used in these studies are acceptable. Other development studies described and performed were: physical characterisation, minimum fill, delivered dose and fine particle mass, single dose fine particle mass, actuator/mouthpiece deposition and delivery device studies. These have followed the EMA guideline. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The product is manufactured using conventional manufacturing techniques for inhalation capsules, consisting of blending the active substance with lactose after which the powder is finally encapsulated. In view of the very low dose and the critical environmental conditions of capsule filling and blister packaging, the process is considered as non-standard. Results of full scale process validation have been provided. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The excipient lactose monohydrate complies with Ph.Eur requirements, a suitable specification for particle size distribution is also applied. 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 product specification includes tests for appearance of dosage form and dose delivery system, identification, assay and pharmaceutical tests (mean delivered dose, uniformity of delivered dose, fine particle dose), impurities, water content and microbiological quality. The release and shelf-life requirements/limits are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided on seven full scale production batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on one pilot scaled and three production scaled batches stored at 25°C/60%RH (24 months), 30°C/75%RH (24 months) and 40°C/75%RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in aluminium-aluminium blisters. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. Out of specification results are reported for fine particle dose for one batch after six months at accelerated conditions. In view of that the product should not be stored above 30°C. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are: 'Do not store above 30°C. Store in the original blister pack in order to protect from moisture'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Tavulus has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Tavulus is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Spiriva which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tiotropium bromide is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

To support this hybrid application, the MAH carried out two pilot bioavailability studies and two pivotal bio-equivalence studies. Furthermore, the MAH performed two peak inspiratory flow (PIF) studies. It should be noted that study 1-3 showed bio-inequivalence to the reference product and were not acceptable. Therefore, no description or results are shown from these studies. The pharmacokinetic study 4 and the two peak inspiratory flow studies were considered acceptable and are thus discussed in detail.

- Study 4: pharmacokinetic studies: pivotal, single dose study, formulation one vs. Spiriva.
- Study 5: peak inspiratory flow (PIF study): pivotal PIF study.
- Study 6: peak inspiratory flow (PIF study): pilot PIF study, single dose, formulations one and three vs. Spiriva

IV.1 Pharmacokinetics

The MAH conducted two pilot bioavailability studies and two bioequivalence studies in which the pharmacokinetic profile of the test product Tavulus (Glenmark s.r.o., Czech Republic) is compared with the pharmacokinetic profile of the reference product Spiriva (Boehringer Ingelheim International GmbH, The Netherlands). As discussed before, only pharmacokinetic study 4 and the PIF studies were considered acceptable and are discussed in this section.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The design of the studies are acceptable.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence studies

Study 4: pharmacokinetic studies: pivotal, single dose study, formulation one vs. Spiriva

Design

This was an open label, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study in healthy adult subjects under fasting conditions. 48 healthy male subjects, aged 20 - 49 years, were dosed in this study. Subjects were divided in two groups. Each subject received a single dose (inhalations of two capsules containing tiotropium bromide inhalation powder (equivalent to 18 µg tiotropium base) delivering about 10 µg per capsule) of both the test and the reference tiotropium formulations. The reference was administered twice. The test was administered by the test device and the reference by the reference device. For each subject there were three dosing periods, separated by a washout period of 55 days.

For reference and test, two inhaler capsules are administered; each capsule will be inhaled by the subjects twice, i.e. the required total number of inhalations for the two inhaler capsules will be four inhalations with a 30-second interval from the start of one inhalation to the other, including breath holding as long as comfortable after each inhalation. In order to minimize errors, the device will be prepared.
First inhalation from the first capsule with holding the breath as long as comfortable, after which normal respiration is resumed by the subject, after 30 seconds.
Second inhalation from the device with the same capsule with holding the breath as long as comfortable after which normal respiration is resumed by the subject, after 30 seconds.
Third inhalation from the second capsule with holding the breath as long as comfortable, after which normal respiration is resumed by the subject, after 30 seconds.
Fourth inhalation from the device with the same capsule with holding the breath as long as comfortable after which normal respiration is resumed by the subject.

Blood samples were taken pre-dose and at 2, 4, 6, 8, 10, 12, 15, 30, 45, minutes and at 1, 2, 4, 6, 8, 10, 12, 24, 48 and 72 hour after inhalation of the powders.

Results

Three subjects withdrew after period I for personal reasons. In total 45 subjects completed the study entirely, and were included in the analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tiotropium bromide under fasted conditions.

Treatment N=45	$AUC_{0-30min}$ (ng.h/ml)	AUC_{0-72h} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test (mean/SD)	2.7 (1.3)	46 (14)	74 (36)	9.6 (6.1)	0.1 (0,03 – 0.17)	54 (32)
Reference (mean/SD)	2.5 (1.3)	45 (16)	69 (33)	9.1 (5.1)	0.1 (0,03 – 0.17)	50 (30)

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
$AUC_{0-30min}$	area under the plasma concentration-time curve from time zero to 30 minutes
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation
SD	standard deviation

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tiotropium bromide under fasted conditions.

Treatment N=45	$AUC_{0-30\ min}$ (ng.h/ml)	$AUC_{0-72\ hours}$ (ng.h/ml)	C_{max} (ng/ml)
Ratio (test/reference) (90% CI)	1.07 (0.98 – 1.17)	1.03 (0.97 – 1.09)	1.07 (0.97 – 1.18)
CV (%)	25.2	16.7	29

$AUC_{0-30min}$	area under the plasma concentration-time curve from time zero to 30 minutes
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
CV	coefficient of variation
CI	confidence interval

Study 5: peak inspiratory flow (PIF study): pivotal PIF study

Design

The study is a single centre, open label, non-significant risk (NSR), non-interventional, crossover, inspiratory flow rate study. This study was performed to collect data on peak inspiratory flow rates (PIFR) of healthy volunteers (HV) and COPD patients when inhaling at maximal inspiratory effort ("quickly and deeply") from the test device and the reference device. The final version of the test device (2), proposed for commercialisation, was used in this study.

This study of the PIF characteristics of HV and COPD patients using the inhaler was intended to:

- Compare the performance of the test device and the reference device in HVs and COPD patients
- Demonstrate that COPD patients could effectively inhale through the devices sufficiently to receive the aerosolised medication (inhalation effectiveness), and thus provide a basis to understand the relevance of data from other sources.
- Understand the difference in inspiratory flow rate performance characteristics between HVs and COPD patients. The results were used to inform the extrapolation of existing data.

Results

All subjects (50 COPD patients and 20 HVs completed the study entirely, and were included in the analysis.

Table 3. Descriptive statistics of PIF rates attained by population and device

Treatment N=X	**Mean (SD)**	**Median (min-max)**	**10^{th} – 90^{th} percentile**	**LS Mean (standard error)**	**Upper/Lower bound (5 – 95 %)**
Test (HV) (N=20)	103.17 (29.91)	97.20 (55.20 – 165.0)	65.16 – 143.40	94.84 (1.06)	85.01 – 105.89
Reference (HV) (N=20)	101.70 (24.90)	101.70 (57.60 – 155.40)	63.24 – 139.80	97.27 (1.06)	87.06 – 108.44
Test (COPD patients) (N=50)	73.04 (16.47)	76.20 (28.20 – 120.60)	48.84 – 91.02	68.23 (1.03)	64.01 – 72.74
Reference (COPD patients) (N=50)	71.54 (15.89)	75.60 (27.00 – 110.40)	47.40 – 87.42	66.83 (1.03)	62.75 – 71.31
CV coefficient of variation **LS** Least Squares **SD** Standard Deviation					

Study 6: peak inspiratory flow (PIF study): pilot PIF study, single dose, formulations one and three vs. Spiriva

Design

This study was designed as a pilot PK study to assess the relative bioavailability of two test formulations in comparison to the reference product, but also inhalation characteristics were measured (PIFR, total inhaled volume and initial flow acceleration). In two study periods subjects inhaled different test formulations via device 1, and in the third period Spiriva via the Handihaler. Subjects were instructed to inhale slowly and deeply.

Results

Table 4. of peak inspiratory flow in healthy volunteers inhaling slowly and deeply

Treatment (N=24)	Mean (SD)	Median	10th percentile	90th percentile
Test	49.18 (7.49)	48.89	39.30	58.63
Reference	46.95 (5.58)	47.25	40.06	55.19
SD standard deviation				

Conclusion on bioequivalence studies

The pharmacokinetic results of the pilot studies 1 and 2 and the pivotal study 3 showed bio-in-equivalence with regard to the test formulation with the same trend in deviations from the exposure variables. As indicated, selection of batches were initially based on the *in vitro* conventional Next Generation Impactor (NGI) method. This method was not able to analyse the Fine Particle Dose (FPD) adequately. After optimising the *in vitro* method, employing an anatomical throat and human breathing profiles method, it appeared that non-acceptable reference batches were used in the pilot studies and in the first pivotal study, i.e. with a large difference in FPD compared to the median value of tested reference and test batches (testing additional reference batches). An *in vitro-in vivo* correlation could be shown with this 'new' method with regard to C_{max} and FPD indicating that the *in vitro* anatomical throat and human breathing profiles method proved to be a better prediction tool. In the pivotal study 4, both test and reference batches were acceptable (i.e. better matching FPD). It has been sufficiently supported that no optimal reference batch was chosen in the second pivotal bioequivalence study and therefore the results obtained in this bioequivalence study is also applicable to other batches of the reference products. It is therefore reasonable to conclude that overall test and reference products are bioequivalent to one another as the second pivotal study is the only equitable comparison amongst those undertaken.

Based on the submitted second bioequivalence study 4, the tiotropium bromide 18 µg inhalation powder delivered by test device is considered bioequivalent with the Spiriva 18 µg inhalation powder delivered by the reference device. The 90% confidence intervals calculated for $AUC_{0\text{-}30min}$ and C_{max} of tiotropium, reflecting the efficacy, and for $AUC_{0\text{-}72h}$, reflection the safety, were inside the normal range of acceptability (0.80 – 1.25).

Based on the submitted bioequivalence studies Tavulus is considered bioequivalent with Spiriva.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Conclusion on PIF studies

The data generated in PIF studies are needed to determine the 10th-50th and 90th percentile generated by healthy volunteers and COPD patients. These flow rates are needed to compare the *in vitro* flow rate dependency between the two inhalers in order to extrapolated the PK data obtained in healthy volunteers to patients. Extrapolation from healthy volunteers to patients is possible, when the products shows *in vitro* the same flow rate dependency for the flows generated by healthy volunteers and patients.

The MAH conducted two clinical studies that compared the PIF flow generated over the test and reference devices. Both studies are not optimally conducted to compare the PIF flow generated over the to be marketed device and the reference inhaler, as no direct comparison is made between the to be marketed inhaler and the reference when patients received the proper inhalation technique (slowly and deeply):

- Study 5 included both COPD patients and healthy volunteers and used the to be marketed inhalation device, device 2. Patients were instructed to inhaled quickly and deeply which results in higher PIF flow rates as compared with the normal inhalation instruction to inhale slowly and deeply.
- Study 6 included only healthy volunteers, and a precursor of the to be marked inhalation device was used i.e. version 1. For COPD patients PIF flows are generated for using the correct inhalation technique.

Nevertheless, the MAH sufficiently justified that the PIF data show, that the generated flows by healthy volunteers and COPD patients over the over the marketed inhalation device 2 would be comparable with the reference considering that:

- PIFRs through the reference and test device in three distinct clinical comparisons were very similar - healthy subjects inhaling slowly and deeply (study 5), healthy subjects inhaling quickly and deeply (study 5) and COPD patients inhaling quickly and deeply (study 5). These results suggest a comparable power transmission between the inhaler and subject when the different inhalation techniques are used.
- The resistance between the two test inhalers (1 and 2) and the reference is comparable while generating similar resistance over different flows.

The inhalation test devices 1 and 2 are comparable. Device 1 was modified to improve the handling, but no modifications were made that may have affected the PIF flow generation. The RMS agrees that based on these considerations, it islikely that COPD patients will generate a comparable PIF flow rate over the device 2 compared with the reference when the proper inhalation technique is used.

Extrapolation from Healthy volunteers to COPD patients.

PIF flow healthy volunteers range 40-65 L/min

The generated PIF flow rates by healthy volunteers with the proper inhalation technique (study 2) shows comparable mean PIF flow rates for the test and reference. With the proper

technique the mean flow is 47 L/min (with 10th percentile 40 L/min and 90th percentile 55 L/min.

PIF flow COPD patients range 36-55 L/min
The MAH provided additional literature that showed that with the COPD population generates mean PIF flows is 4 L/min, (with 10th percentile 36 L/min and 90th percentile 54 L/min) with the reference product. Considering the above considerations, these flows will also be likely be generated with inhaler 2 in COPD patients when the proper inhalation technique is applied i.e. inhale slowly and deeply.

Same flow rate dependency test and reference for range 20-60L/min
The *in vitro* data show that test and reference product have a same flow rate dependency for the flow tested for 20 L/min, 40 L/min and 60 L/min. These are the flows that will be generated by healthy volunteers and COPD patients with the proper inhalation technique over inhaler 2 and the reference. The constant flow rate dependency between these two inhalers support that the PK data obtained in healthy volunteers can be extrapolated to COPD patients.

In conclusion, the MAH sufficiently justified that the generated PIF flows rates over the to be marketed inhaler will be comparable with the reference product for both the healthy volunteers and COPD patients when they inhale slowly and deeply. The products have a same flow rate dependency for the generated PIF flows in healthy volunteers and COPD patients. This makes the extrapolation of the PK data obtained in healthy volunteers to COPD possible.

IV.2 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Tavulus.

Table 5. Summary table of safety concerns as approved in RMP

Important identified risks	• None
Important potential risks	• Cardiac mortality • Cardiac disorders (ischaemic heart disease including myocardial infarction and angina pectoris, cardiac arrhythmia, cardiac failure)
Missing information	• Pregnant and breast-feeding women • Patients with a recent history of myocardial infarction, unstable or life-threatening cardiac arrhythmia, paroxysmal tachycardia and decompensated heart failure

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Spiriva. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Furthermore, the MAH submitted two PIF studies in which was concluded that the PIFR from healthy adults could be extrapolated to COPD patients. This was also considered acceptable. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the PL of Tiogiva 18 microgram, inhalation powder, hard capsule (Sweden, SE/H/1924/001/DC) (parent PL) The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tavulus 18 microgram, inhalation powder in hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Spiriva 18 microgram inhalation powder in hard capsules. Spiriva is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

A board meeting was held on the 1st of April which aimed to discuss the stability of the drug product outside of the blister packaging. After the MAH sent in additional stability studies this issue was considered solved. No other issues remained.

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 essential similarity has been demonstrated for Tavulus with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 April 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse