Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

TIOGIVA 18 MICROGRAM, INHALATION POWDER, HARD CAPSULE
tiotropium bromide, anhydrous

PL 25258/0370

Glenmark Pharmaceuticals Europe Limited

LAY SUMMARY

Tiogiva 18 microgram, inhalation powder, hard capsule
tiotropium bromide, anhydrous

This is a summary of the Public Assessment Report (PAR) for Tiogiva 18 microgram, inhalation powder, hard capsule. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Tiogiva inhalation powder in this lay summary for ease of reading.

For practical information about using Tiogiva inhalation powder, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Tiogiva inhalation powder and what is it used for?
This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the United Kingdom (UK) called Spiriva 18 microgram inhalation powder.

Tiogiva inhalation powder is used to help people who have chronic obstructive pulmonary disease (COPD).

How does Tiogiva inhalation powder work?
This medicine contains the active ingredient tiotropium bromide, which is a long-acting bronchodilator. It works by helping to open the airways and making it easier to get air in and out of the lungs.

How is Tiogiva inhalation powder used?
The pharmaceutical form of this medicine is an inhalation powder, hard capsule, and the route of administration is inhalation.

The recommended dose is 1 capsule (18 micrograms of tiotropium) once a day, inhaled with the dry powder inhaler. Patients should not use more than the recommended dose. Tiogiva inhalation powder is not recommended for children and adolescents under 18 years.

Patients should try to use the capsule at the same time every day. This is important because Tiogiva inhalation powder is effective over 24 hours.

The capsules are only for inhalation and not for oral intake. Patients should not swallow the capsules. Detailed instructions, including pictograms, on how to use the dry powder inhaler are provided in the PIL.

The dry powder inhaler (MRX003-R), which patients should put the Tiogiva inhalation powder capsule into, makes holes in the capsule and allows the patient to breathe in the powder.

Patients should make sure that they have a dry powder inhaler and that they can use it properly. The instructions for use of the dry powder inhaler are provided in the PIL.

Patients should not blow into the dry powder inhaler. They should clean the dry powder inhaler once a month. Cleaning instructions for the dry powder inhaler are provided in the PIL.

When taking Tiogiva inhalation powder, patients should take care not to let any of the powder enter their eyes. If any powder does get into the eyes, patients may get blurred vision, eye pain and/or red eyes. Patients should wash their eyes in warm water immediately. Then talk to their doctor immediately for further advice. If the patient feels that their breathing is worsening, they should tell their doctor as soon as possible.

For further information on how Tiogiva inhalation powder is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Tiogiva inhalation powder have been shown in studies?
Because Tiogiva inhalation powder is a hybrid medicine, data from *in vitro* tests and pharmacokinetic (PK) studies in healthy volunteers were used to determine that it has comparable efficacy and safety to that of the reference medicine.

What are the possible side effects of Tiogiva inhalation powder?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Tiogiva inhalation powder is a hybrid medicine, data from *in vitro* tests and PK studies in healthy volunteers were used to determine that it has comparable efficacy and safety to that of the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the SmPC available on the MHRA website.

Why was Tiogiva inhalation powder approved?
It was concluded that Tiogiva inhalation powder has been shown to have comparable efficacy and safety to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Tiogiva inhalation powder?
A Risk Management Plan (RMP) has been developed to ensure that Tiogiva inhalation powder is used as safely as possible. Based on this plan, safety information has been included in

the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Tiogiva inhalation powder

A Marketing Authorisation for Tiogiva inhalation powder was granted in the UK on 07 April 2021 to ELC-Group Limited (PL 45134/0006).

The licence underwent a Change of Ownership to Glenmark Pharmaceuticals Europe Limited on 17 May 2021.

The full PAR for Tiogiva inhalation powder follows this summary.

This summary was last updated in June 2021.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Tiogiva 18 microgram, inhalation powder, hard capsule (PL 25258/0370) could be approved.

The product is approved for the following indication:
As a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).

Tiotropium bromide is a long-acting, specific, muscarinic receptor antagonist, in clinical medicine often called an anticholinergic. By binding to the muscarinic receptors in the bronchial smooth musculature, tiotropium bromide inhibits the cholinergic (bronchoconstrictive) effects of acetylcholine, released from parasympathetic nerve endings. It has similar affinity to the subtypes of muscarinic receptors, M1 to M5.

In the airways, tiotropium bromide competitively and reversibly antagonises the M3 receptors, resulting in relaxation. The effect is dose dependent and lasts longer than 24h. The long duration is probably due to the very slow dissociation from the M3 receptor, exhibiting a significantly longer dissociation half-life than ipratropium. As an N-quaternary anticholinergic, tiotropium bromide is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before systemic anticholinergic effects may occur.

This application was approved under Regulation 52B of The Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be a hybrid medicinal product of a suitable originator product, Spiriva 18 microgram inhalation powder, that has been licensed within the UK for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a hybrid medicinal product of a suitable reference product.

Data from 5 clinical studies were submitted with this application. These studies were conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 23 April 2020 because of matters relating to quality, safety and efficacy. Further data was submitted by the applicant and was considered by the CHM on 21 January 2021. The issues were considered to be resolved and the grant of a Marketing Authorisation was advised.

A national marketing authorisation was granted in the United Kingdom (UK) on 07 April 2021 to ELC-Group Limited (PL 45134/0006). The licence underwent a Change of Ownership to Glenmark Pharmaceuticals Europe Limited on 17 May 2021.

II QUALITY ASPECTS

II.1 Introduction

This product consists of transparent colourless hard capsules containing the inhalation powder, with 'T10' printed on the capsules.

Each capsule contains 21.7 micrograms of tiotropium bromide, anhydrous (amorphous), equivalent to 18 micrograms of tiotropium.

The delivered dose (the dose that leaves the mouthpiece) is 12.1 micrograms of tiotropium bromide, anhydrous (amorphous) equivalent to 10 micrograms of tiotropium.

In addition to tiotropium bromide, anhydrous, this product also contains the following excipients:
- Lactose monohydrate (which may contain small amounts of milk proteins).
- Capsule composed of hydroxypropylmethylcellulose (HPMC), commonly known as Hypromellose.
- Capsule printing ink: Shellac, black iron oxide, propylene glycol, strong ammonia solution, potassium hydroxide

The finished product is packaged in an aluminium/aluminium peel-off blister containing 10 capsules. The blisters are supplied in a cardboard box and, depending on the pack, the box will also contain a dry powder inhaler.

The dry powder inhaler is a single dose inhalation device made from acrylonitrile butadiene styrene plastic materials and stainless steel.

The finished product is presented in the following pack sizes:
- Cardboard box containing 30 capsules (3 blisters) with a dry powder inhaler
- Cardboard box containing 60 capsules (6 blisters) with a dry powder inhaler
- Cardboard box containing 90 capsules (9 blisters) with a dry powder inhaler

- Cardboard box containing 30 capsules (3 blisters)
- Cardboard box containing 60 capsules (6 blisters)
- Cardboard box containing 90 capsules (9 blisters)

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

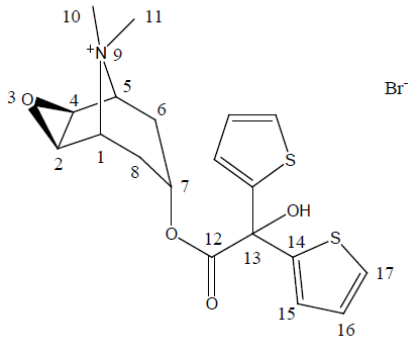
rINN: Tiotropium bromide

Chemical Names: (1α,2β,4β,7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-9-ium bromide

(1R,2R,4S,5S,7s)-7-[(hydroxy[di(thiophen-2-yl)]acetyl)oxy]-9,9-dimethyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-9-ium bromide

Molecular Formula: $C_{19}H_{22}BrNO_4S_2$ (anhydrous)

Chemical Structure:



Molecular Weight: 472.4 (anhydrous)
Appearance: Brownish to off white powder, anhydrous substance
Solubility: Soluble in phosphoric acid, monosodium phosphate, disodium phosphate, and in methanol. Practically insoluble in dichloromethane and freely soluble in dimethylsulfoxide.

Tiotropium bromide, anhydrous, is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

In accordance with the CHMP Guideline for Orally Inhaled Products (CPMP/EWP/4151/00 Rev. 1), the following comparative *in vitro* testing was performed using batches of the test and reference product: dissolution testing, aerodynamic particle size distribution testing and delivered dose testing. Comparative impurity profiles have also been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months, with the storage conditions of 'Do not store above 30°C', is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of tiotropium bromide are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology
No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this is a hybrid application of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
In accordance with the regulatory requirements, data from five clinical studies have been submitted with this application. These include two pilot and two pivotal pharmacokinetic studies and one study to characterise inspiratory flow rate characteristics in COPD patients. These studies were conducted in-line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following studies.

Peak Inspiratory Flow (PIF) study
This study was an open label, single-centre, cross-over study designed to characterise peak inspiratory flow rates obtained while inhaling through MRX003-T10 (test device) and HandiHaler (reference device) in healthy volunteers and in patients with COPD.

A total of 70 subjects were enrolled in the study (Cohort A = Healthy Volunteers, n=20, Cohort B = COPD patients, n=50). Eligible subjects underwent spirometry and were trained by healthcare professional on how to perform a forced inspiratory manoeuvre to ensure the participants would use the correct inhalation technique

The subjects then performed the PIF test for each device (connected to a spirometer) on 3 occasions in an alternate fashion. Empty capsules were used in the devices for the PIF measurements.

The study end points were as follows:
Primary end point:
- Peak Inspiratory Flow rate (PIF)

Secondary end points:
- Time to PIF attained through test and reference devices
- Acceleration to PIF attained through test and reference devices
- Time of inhalation (s)
- Inspired Volume (L)/ Forced Inspiratory Vital Capacity (FIVC)

A summary of the study results are presented below:

Descriptive statistics for PIF rates

Cohort		Healthy Volunteer		COPD Patients	
Test Device		HandiHaler	MRX003-T10	HandiHaler	MRX003-T10
Sample (N)		20	20	50	50
PIF characteristics (L/min)	Mean	101.70	103.170	71.54	73.04
	Standard Deviation	24.90	29.91	15.89	16.47
	Median	101.70	97.20	75.60	76.20
	Min	57.60	55.20	27.00	28.20
	Max	155.40	165.0	110.40	120.60
	10^{th} percentile	63.24	65.16	47.40	48.84
	90^{th} percentile	139.80	143.4	87.42	91.02
Log-transformed values[8]	LS Mean	97.27	94.84	66.83	68.23
	Standard error	1.06	1.06	1.03	1.03
	Lower bound 5%	87.06	85.01	62.75	64.01
	Upper bound 95%	108.44	105.89	71.31	72.74

There was no statistically significant differences identified on the PIF rates attained by the subjects between the test and reference products in both the cohorts.

There were no statistically significant differences within the moderate, severe or very severe disease severity categories (classified at screening pre-bronchodilation) for the tested devices for PIF rate, time to PIF, acceleration to PIF, inhalation time or the inhaled volume (FIVC/ IV) values.

For the secondary end points of the study, no statistically significant differences were observed for time to PIF, acceleration to PIF, inhalation times or the FIVC/IV between the test and reference devices in either of the cohorts of subjects.

Pilot study 1
This study was an open label, randomised, single inhaled dose, three-way cross over comparative pharmacokinetic pilot study between different dry powdered inhalation formulations of tiotropium. The study was conducted in healthy volunteers.

The dose of tiotropium was two capsules (20 µg delivered dose). Each capsule was administered in two inhalations. The wash out period was at least 2 weeks.

Eligible subjects were randomised to receive one of the three treatments in each period:
- Treatment A: 20 µg tiotropium as Test formulation 1 (2 capsules, each with a delivered dose of about 10 µg tiotropium, inhaled via the MRX003 inhalation device)
- Treatment B: 20 µg tiotropium as Test formulation 2 (2 capsules, each with a delivered dose of about 10 µg tiotropium, inhaled via the MRX003 inhalation device)
- Treatment C: 20 µg tiotropium as Reference product, Spiriva 18 microgram inhalation powder (2 capsules, each with a delivered dose of 10 µg tiotropium, inhaled via the Handihaler device)

Subjects were trained on the correct use of inhaler before the study treatment administration.

Blood samples for determination of tiotropium were collected pre-dose and up to 144 hours after the last inhalation in each study period.

A summary of the pharmacokinetic results are presented below:

ANCOVA results for the comparison for test and reference formulations

Based on PK Dataset

Parameter	Trt	n	Arithmetic Mean (CV%)	Geometric Mean	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%)
AUC_t	A	18	89.957 (32)	85.023	A vs C	112.18	101.89 - 123.51	17
(hr*pg/mL)	B	18	176.907 (22)	172.120	B vs C	227.10	206.26 - 250.04	17
	C	18	81.539 (36)	75.791	A vs B	49.40	44.86 - 54.39	17
AUC_{inf}	A	18	116.678 (34)	109.494	A vs C	111.71	102.30 - 121.99	16
(hr*pg/mL)	B	18	228.152 (26)	220.063	B vs C	224.52	205.60 - 245.18	16
	C	18	104.650 (34)	98.014	A vs B	49.76	45.56 - 54.33	16
C_{max}	A	18	8.507 (37)	7.878	A vs C	131.82	112.31 - 154.72	29
(pg/mL)	B	18	17.452 (33)	16.494	B vs C	275.97	235.13 - 323.91	29
	C	18	6.815 (52)	5.977	A vs B	47.77	40.70 - 56.06	29
$AUC_{0-0.5}$	A	18	2.495 (33)	2.355	A vs C	132.03	116.42 - 149.73	23
(hr*pg/mL)	B	18	5.429 (32)	5.169	B vs C	289.83	255.56 - 328.69	23
	C	18	1.947 (40)	1.783	A vs B	45.56	40.17 - 51.66	23
		n	Median	Range				
T_{max}	A	18	0.14	0.06- 4.05				
(hr)	B	18	0.11	0.06- 0.18				
	C	18	0.10	0.06- 4.05				

Amongst the two test formulations, Treatment A demonstrated comparable total exposure to the reference formulation, although the 90% CIs around the ratio of geometric means for Cmax and AUC0-0.5 (or AUC0-30min) was roughly 32% higher compared to the reference product.

Treatment B demonstrated significantly higher exposure than the reference, and was not considered further by the Applicant.

Pilot study 2

This study was an open label, randomised, single dose, three-period, cross over comparative pharmacokinetic pilot study between different dry powdered inhalation formulations of tiotropium. The study was conducted in healthy volunteers.

The dose of tiotropium was one capsule (10 µg delivered dose) which was administered in two inhalations. The wash out period was 25 days.

Eligible subjects were randomised to receive one of the three treatments in each period:

- Treatment A: 10 µg tiotropium as Test formulation 1 (1 capsule with a delivered dose of about 10 µg tiotropium, inhaled via the MRX003 inhalation device)
- Treatment B: 10 µg tiotropium as Test formulation 2 (1 capsule with a delivered dose of about 10 µg tiotropium, inhaled via the MRX003 inhalation device)
- Treatment C: 10 µg tiotropium as Reference product, Spiriva 18 microgram inhalation powder (1 capsule with a delivered dose of 10 µg tiotropium, inhaled via the Handihaler device)

Subjects were trained on the correct use of inhaler before the study treatment administration.

Blood samples for determination of tiotropium were collected pre-dose and up to 24 hours post dose. Time zero was defined as being when the first of 2 inhalations was completed (two inhalations were performed per capsule).

A summary of the pharmacokinetic results are presented below:

Bioequivalence Confidence Intervals and Intrasubject CV% of tiotropium for the Test A/Reference C

Parameter	90% Confidence interval			Intrasubject CV% (Logarithmic)*
	Point estimate %	Lower Limit %	Upper Limit %	
C_{max}	83.12	71.38	96.80	32.19
$AUC_{0\to t}$	96.39	90.05	103.18	14.10
$AUC_{0\to\infty}$	91.86	79.46	106.20	30.57

Bioequivalence Confidence Intervals and Intrasubject CV% of tiotropium for the Test B/Reference C

Parameter	90% Confidence interval			Intrasubject CV% (Logarithmic)*
	Point estimate %	Lower Limit %	Upper Limit %	
C_{max}	73.47	63.09	85.56	32.19
$AUC_{0\to t}$	105.72	98.77	113.17	14.10
$AUC_{0\to\infty}$	91.31	78.98	105.56	30.57

This study also demonstrated a comparable total systemic exposure between the Test Treatment A and the reference product, however the use of a short sampling time of 24 hours was deemed inadequate for tiotropium. The Cmax, in contrast to the results from the first pilot study, was lower for Test treatment A than the reference product.

The comparative results for Treatment B versus reference product were similar to Treatment A, except that the difference for Cmax was even higher for this formulation.

As the pilot studies were designed to facilitate the selection of Test formulation for the pivotal pharmacokinetic study, and as the first pilot study used a Test device version significantly different than the final version used in the pivotal studies, no inferences are drawn from these results on the pharmacokinetic equivalence between the Test and Reference products.

Pivotal study 1

This study was an open label, randomised, single dose, three-period, partial replicate (two reference periods), cross-over study in healthy volunteers comparing the test product Tiogiva 18 microgram, inhalation powder, hard capsule (Test formulation A in the pilot studies), delivered via the test MRX003-T10 inhaler, with the reference product, Spiriva 18 microgram inhalation powder, delivered via the reference product inhaler device, the Handihaler. The study was conducted in healthy volunteers.

The dose of tiotropium was two capsules (20 µg delivered dose). Each capsule was administered in two inhalations. The wash out period was at least 25 days.

Blood samples were collected pre-dose and up to 72 hours post-dose. Time zero was defined as being when the first of 4 inhalations was completed.

A summary of the pharmacokinetic results are presented below:

ANCOVA results

Parameter	90% Confidence interval		
	Point estimate %	Lower Limit %	Upper Limit %
C_{max}	130.36	122.53	138.69
$AUC_{0\to t}$	114.06	110.69	117.52
$AUC_{0\to 30}$	125.13	118.77	131.83

Intra-subject CV% of Cmax of the Reference product

Parameter	Intrasubject CV% (Logarithmic)*
C_{max}	23.06

The 90% Confidence Intervals (CIs) around the ratio of geometric means for Cmax and AUC0-30 were outside the 80-125% acceptability limits. Therefore, pharmacokinetic equivalence was not demonstrated between the test and reference products. For AUC0-t, the 90% CIs were within the acceptability limits.

As the intra-subject CV for reference Cmax was <30%, the adjustment to the acceptability limits for Cmax was not applicable.

Pivotal study 2

This was the second pivotal study conducted comparing the test and reference products, as the first study failed to demonstrate pharmacokinetic equivalence. The study was also an open-label, randomised, single dose, cross-over trial and the design elements were very similar to the first pivotal study, except the study included only a single reference period and had an extended washout period.

The dose of tiotropium was two capsules (20 µg delivered dose). Each capsule was administered in two inhalations. The wash out period was at least 55 days.

Blood samples were collected pre-dose and up to 72 hours post-dose. Time zero was defined as being when the first of 4 inhalations was completed.

A summary of the pharmacokinetic results are presented below:

ANCOVA results

Parameter	90% Confidence interval			
	Point estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)*
C_{max}	106.78	96.56	118.09	28.98
$AUC_{0\to t}$	102.72	96.85	108.95	16.72
$AUC_{0\to 30min}$	106.77	97.78	116.58	25.18

The 90% CIs around the ratio of geometric means for Cmax, AUC0-t and AUC0-30min were within the 80-125% acceptability limits. Therefore, bioequivalence was demonstrated between the test and reference products.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data have been submitted for this application and none were required.

IV.5 Clinical safety

With the exception of the safety data from the clinical studies submitted with this application, no new safety data were submitted. The safety data submitted showed that the product was well-tolerated. No new or unexpected safety issues were raised from these data.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified.

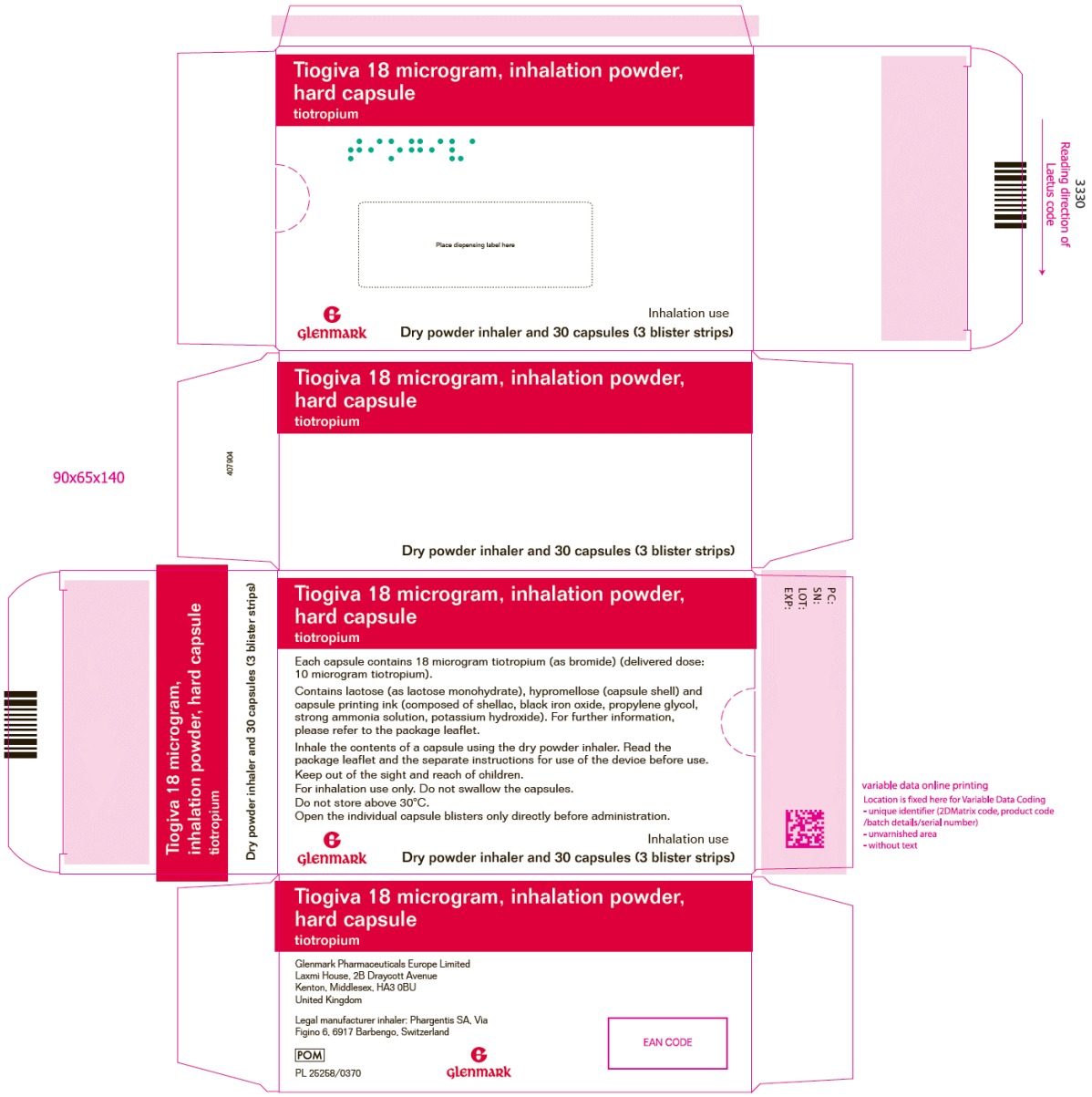
Extensive clinical experience with tiotropium bromide is considered to have demonstrated the therapeutic value of the product.

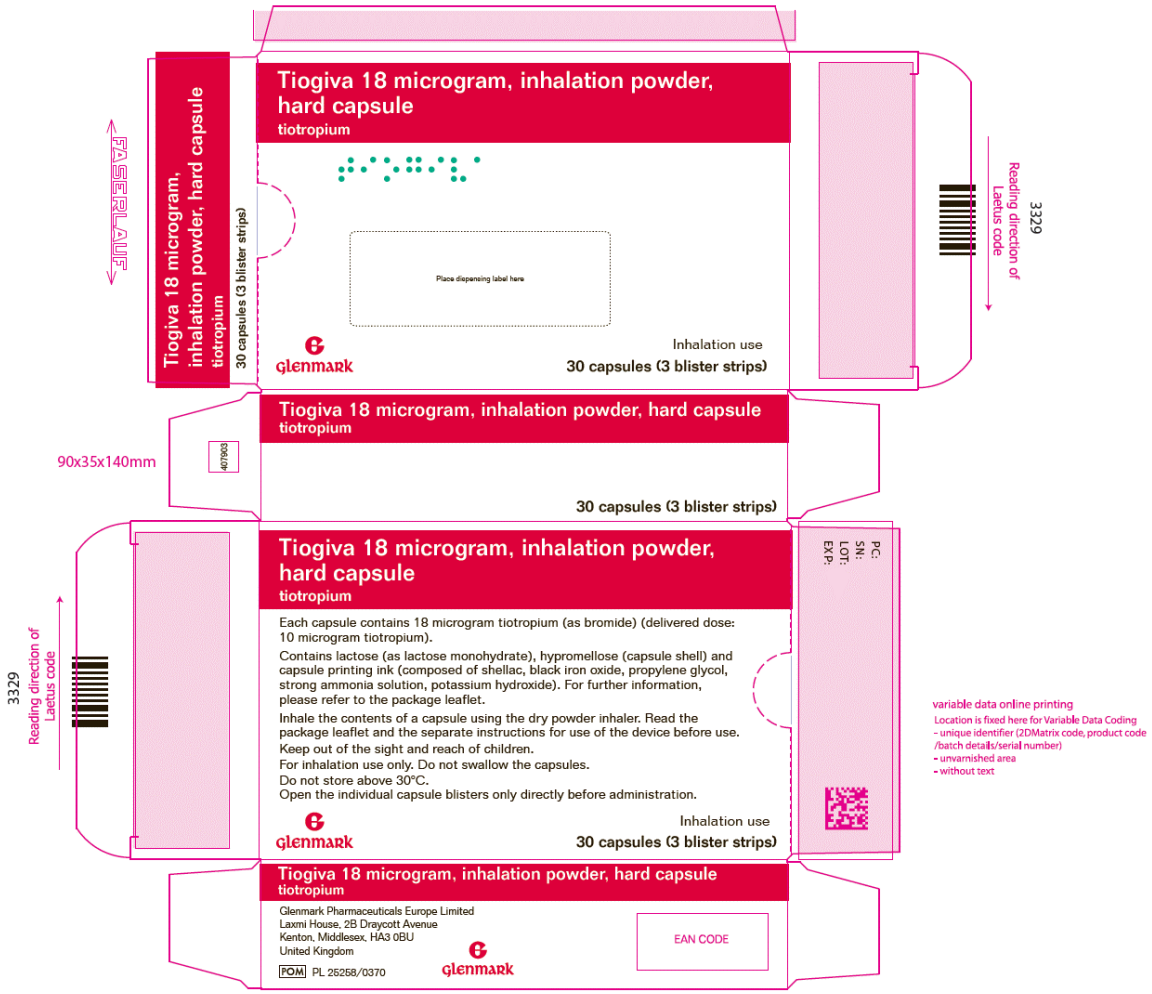
The benefit/risk is, therefore, considered to be positive.

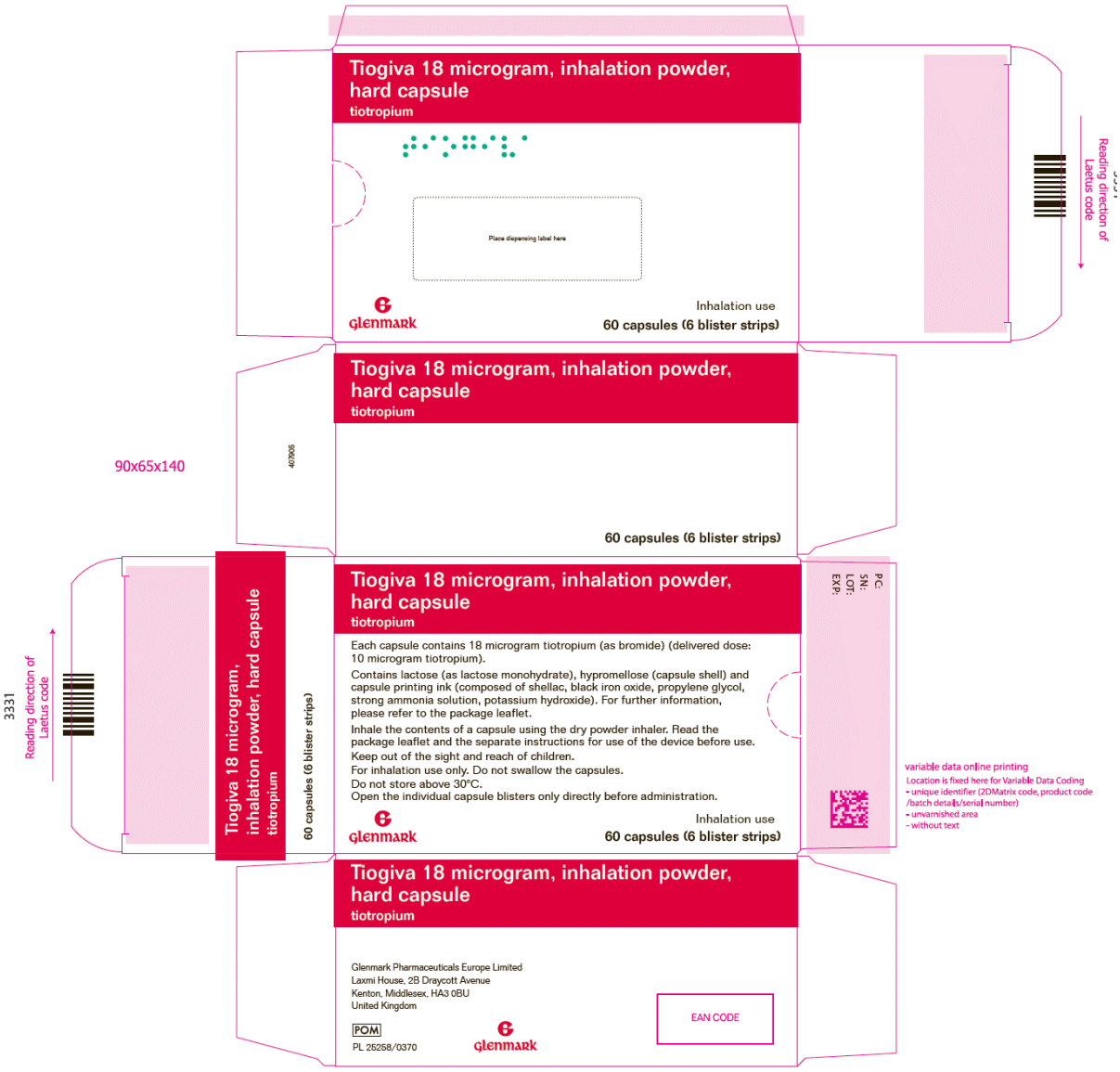
The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines.

In accordance with Regulation 203(2) of The Human Medicines Regulation 2012, as amended, the current approved versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing (following the Change of Ownership) are provided below.




Tiogiva 18 microgram, inhalation powder, hard capsule
tiotropium
FASERLAUF
Tiogiva 18 microgram, inhalation powder, hard capsule
tiotropium
30 capsules (3 blister strips)
Place dispensing label here
glenmark
Inhalation use
30 capsules (3 blister strips)
3329
Reading direction of Laetus code
90x35x140mm
407603
PC:
SN:
LOT:
EXP:
Each capsule contains 18 microgram tiotropium (as bromide) (delivered dose: 10 microgram tiotropium).
Contains lactose (as lactose monohydrate), hypromellose (capsule shell) and capsule printing ink (composed of shellac, black iron oxide, propylene glycol, strong ammonia solution, potassium hydroxide). For further information, please refer to the package leaflet.
Inhale the contents of a capsule using the dry powder inhaler. Read the package leaflet and the separate instructions for use of the device before use.
Keep out of the sight and reach of children.
For inhalation use only. Do not swallow the capsules.
Do not store above 30°C.
Open the individual capsule blisters only directly before administration.
variable data online printing
Location is fixed here for Variable Data Coding
- unique identifier (2DMatrix code, product code /batch details/serial number)
- unvarnished area
- without text
Glenmark Pharmaceuticals Europe Limited
Laxmi House, 2B Draycott Avenue
Kenton, Middlesex, HA3 0BU
United Kingdom
POM PL 25258/0370
EAN CODE


Tiogiva 18 microgram, inhalation powder, hard capsule
tiotropium
Place dispensing label here
glenmark
Inhalation use
60 capsules (6 blister strips)
Reading direction of Laetus code
90x65x140
407005
Tiogiva 18 microgram, inhalation powder, hard capsule
tiotropium
60 capsules (6 blister strips)
PC:
SN:
LOT:
EXP:
Each capsule contains 18 microgram tiotropium (as bromide) (delivered dose: 10 microgram tiotropium).
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3331
Reading direction of Laetus code
Tiogiva 18 microgram, inhalation powder, hard capsule
tiotropium
60 capsules (6 blister strips)
variable data online printing
Location is fixed here for Variable Data Coding
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Laxmi House, 2B Draycott Avenue
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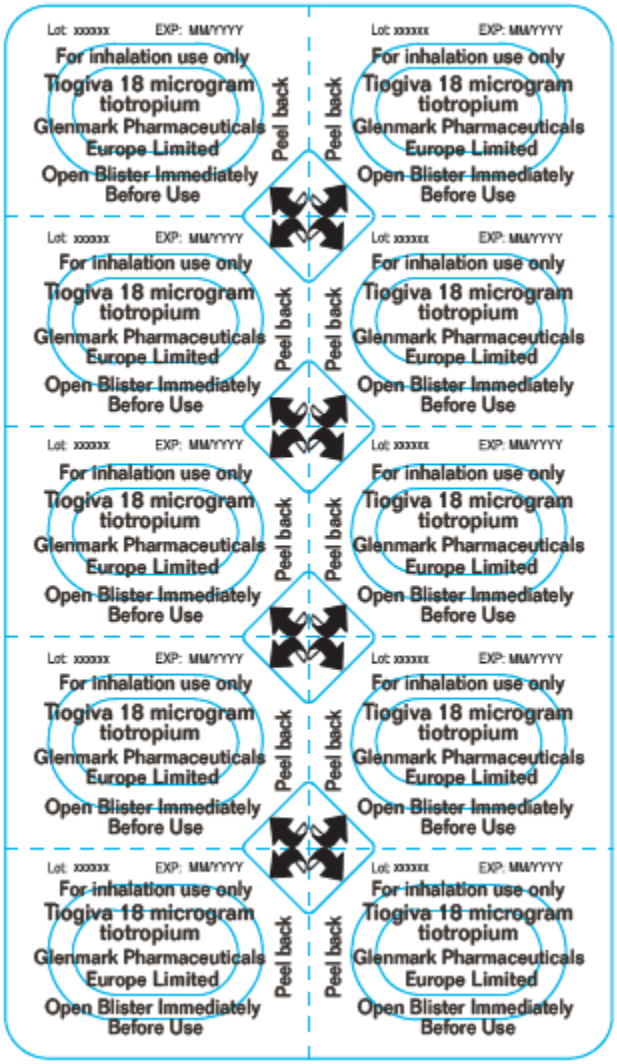
Lot: xxxxxx EXP: MM/YYYY
For inhalation use only
Tiogiva 18 microgram
tiotropium
Glenmark Pharmaceuticals
Europe Limited
Open Blister Immediately
Before Use
Peel back

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**