Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Spironolactone 12.5 mg Film-coated Tablets
Spironolactone 25 mg Film-coated Tablets
Spironolactone 50 mg Film-coated Tablets
Spironolactone 100 mg Film-coated Tablets

(spironolactone)

PL 12762/0544-0547

Mercury Pharmaceutical Limited

LAY SUMMARY

Spironolactone 12.5 mg Film-coated Tablets
Spironolactone 25 mg Film-coated Tablets
Spironolactone 50 mg Film-coated Tablets
Spironolactone 100 mg Film-coated Tablets

(spironolactone)

This is a summary of the Public Assessment Report (PAR) for Spironolactone 12.5 mg, 25 mg, 50 mg and 100 mg Film-coated Tablets.

It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Spironolactone Film-coated Tablets in this lay summary for ease of reading.

For practical information about using Spironolactone Film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Spironolactone Film-coated Tablets and what are they used for?
The applications for Spironolactone 25 mg, 50 mg and 100 mg Film-coated Tablets are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised in the European Union (EU) called Aldactone 25 mg, 50 mg and 100 mg Film-coated Tablets.

The application for Spironolactone 12.5 mg Film-coated Tablets is for a hybrid medicine. This means that the medicine is similar to the reference medicine Aldactone 100 mg Film-coated Tablets, albeit with certain differences. In this case, Spironolactone 12.5 mg film-coated tablets, are a lower strength (of the active substance), than the reference product.

Spironolactone Film-coated Tablets are used in the treatment of the following illnesses:
- “nephrotic syndrome” - a kidney disorder that causes too much fluid in the body
- “ascites” - too much fluid in the abdomen and “oedema” - accumulation of fluid beneath skin or in one or more cavities of the body that produces swelling, for example caused by cirrhosis of the liver.
- “malignant ascites” - fluid containing cancer cells that collect in the abdomen
- “primary aldosteronism” - extra fluid in the body caused by too much of a hormone called “aldosterone”.

Children should only be treated under guidance of a paediatric specialist.

How do Spironolactone Film-coated Tablets work?
Spironolactone, the active substance, belongs to a group of medicines called ‘diuretics’ (also known as ‘water’ tablets).

Patients taking these medicines may have gone to their doctor because they had swollen ankles or were short of breath. This can happen when the heart's pumping action has become weak because of too much fluid in the body. This is called “congestive heart failure”. Pushing extra fluid around the body means the patient’s heart has to work harder.

Spironolactone works to help patients, with any of the diseases listed above, to get rid of the extra fluid from the body as urine and help the patient’s heart to have to do less work.

How are Spironolactone Film-coated Tablets used?
The pharmaceutical form of these medicines are film-coated tablets and the route of administration is oral (taken by mouth).

Recommended dose
These medicines should be taken once a day with food.

Adults
The adult dose varies from 25 mg to 400 mg spironolactone a day, depending on the condition being treated. The patient should ask their doctor if they are not sure how much medicine to take.

Elderly
The patient's doctor will start their patient on a low starting dose and gradually increase the dosage as needed to obtain the desired effect.

Use in children and adolescents
The number of tablets a caregiver will give to a child will depend on the child's weight. The child's doctor will work out the number of tablets that the caregiver should give.

The patient must talk to a doctor if they do not feel better or if they feel worse.

For further information on how Spironolactone Film-coated Tablets are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take these medicines 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 Spironolactone Film-coated Tablets have been shown in studies?
Because Spironolactone Film-coated Tablets are generic medicines and a hybrid medicine for an additional strength, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Spironolactone Film-coated Tablets?
Because Spironolactone Film-coated Tablets are generic/hybrid medicines, the benefits and possible side effects are considered to be the same as for the reference medicines.

For the full list of all side effects reported with these medicines, see Section 4 of the package leaflet or the Summaries of Product Characteristics (SmPCs) available on the MHRA website.

Why were Spironolactone Film-coated Tablets approved?
It was concluded that, in accordance with EU requirements, Spironolactone Film-coated Tablets have been shown to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, 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 Spironolactone Film-coated Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Spironolactone Film-coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflet, 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 Spironolactone Film-coated Tablets
Marketing Authorisations for Spironolactone Film-coated Tablets were granted in the UK on 04 August 2020.

The full PAR for Spironolactone Film-coated Tablets follows this summary.

This summary was last updated in September 2020.

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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 applications for Spironolactone 12.5 mg, 25 mg, 50 mg and 100 mg film-coated tablets (PL 12762/0544-547) could be approved.

The products are approved for the following indications:

- •congestive cardiac failure
- •hepatic cirrhosis with ascites and oedema
- •malignant ascites
- •nephrotic syndrome
- •diagnosis and treatment of primary aldosteronism.

Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available.

The active substance, spironolactone, is a competitive aldosterone antagonist. It increases sodium excretion whilst reducing potassium loss at the distal renal tubule. It has a gradual and prolonged action.

The applications for Spironolactone 25 mg, 50 mg and 100 mg film-coated Tablets were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic medicines of suitable originator medicinal products, Aldactone 25 mg, 50 mg and 100 mg Film-coated Tablets, that have been licensed within the EU for a suitable time, in line with the legal requirements.

The application for Spironolactone 12.5 mg film-coated Tablets was submitted under Article 10(3) of Directive 2001/83/EC, as amended, claiming to be a hybrid medicinal product of the suitable originator medicinal product, Aldactone 100 mg Film-coated Tablets.

No new non-clinical studies were conducted, which is acceptable given that the applications are based on being generic/hybrid medicinal products of reference products that have been licensed for over 10 years.

With the exception of one bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are based on being generic/hybrid medicinal products of a reference product that has been in clinical use for over 10 years. The bioequivalence study was 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 these products at all sites responsible for the manufacture, assembly and batch release of these products.

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

Advice was sought from the Commission of Human Medicines (CHM) on 23 April 2020 and 16 July 2020 because major objections were raised with respect to quality and clinical aspects of the dossier. The Committee provisionally concluded that further information on quality and clinical aspects should be requested before the products could be approved. In response to the CHM advice, the applicant provided additional data, to address the points that had been raised. Following consideration of the responses and further data that were submitted, the approval of the marketing authorisations was recommended.

Marketing Authorisations were granted for these products on 04 August 2020.

II QUALITY ASPECTS

II.1 Introduction

These products contain 12.5 mg, 25 mg, 50 mg or 100 mg of spironolactone in each film-coated tablet.

In addition to spironolactone, these products also contain the excipients lactose monohydrate, calcium sulphate dihydrate, crospovidone, povidone, maize starch, magnesium stearate, hypromellose, titanium dioxide and polyethylene glycol.

The finished products are packaged in:

(1) polyvinylchloride/foil blisters containing 100 or 500 film-coated tablets
(2) polyvinylchloride/foil blisters, in calendar packs of 28 film-coated tablets

Not all pack sizes may be marketed.

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

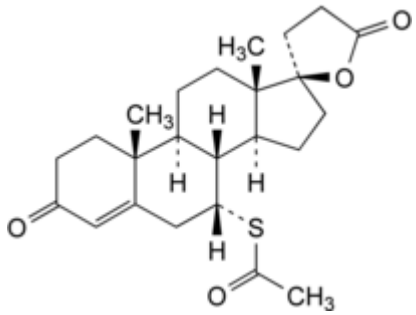
II.2 ACTIVE SUBSTANCE

rINN: Spironolactone

Chemical Name: S-[(2′R)-3,5′-Dioxo-3′,4′-dihydro-5′H-spiro[androst-4-ene-17,2′-furan]-7α-yl] ethanethioate

Molecular Formula: $C_{24}H_{32}O_4S$

Chemical Structure:



Molecular Weight: 416.6 g/mol

Appearance: White or yellowish-white powder.

Solubility: Practically insoluble in water, soluble in ethanol (96 per cent).

Spironolactone is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have 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.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

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

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

Finished Product Specifications
The finished product specifications 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 2 years, with the storage conditions 'This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.', are 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 Marketing Authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of spironolactone 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 these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic/hybrid versions of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of Marketing Authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of spironolactone are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for applications of this type. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the applications, the applicant submitted the following bioequivalence study.

Study 0683-17

This study was an open-label, randomised, two-sequence, two-treatment, two-period, single oral dose, crossover bioequivalence study comparing the test product Spironolactone 100 mg film-coated tablets and the reference product Aldactone (Spironolactone tablets 100 mg) in healthy, adult, male subjects under fed conditions.

After an overnight fast of at least 10 hours, subjects were administered a single dose (100 mg) of either treatment with approximately 240 ml of water 30 minutes after a high fat, high calorie breakfast. Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of seven days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1: Summary of Pharmacokinetic Parameters for Spironolactone

Parameters	Geometric LSM		**Ratio (T/R)%**	**90% CI Lower**	**90% CI Upper**
	Test (T)	Reference (R)			
C_{max} (ng/mL)	136.892	135.245	101.2	94.56	108.34
AUC_{0-t} (ng.h/mL)	358.598	344.568	104.1	100.16	108.14
AUC_{0-inf} (ng.h/mL)	369.987	355.668	104.0	100.12	108.09

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the 100 mg strength test and reference products.

As the 12.5 mg, 25 mg and 50 mg strengths of the test product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 100 mg strength tablet can be extrapolated to the other strengths.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, 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 Marketing Authorisations is recommended for these applications.

V USER CONSULTATION

The Patient Information Leaflet (PIL) 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 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

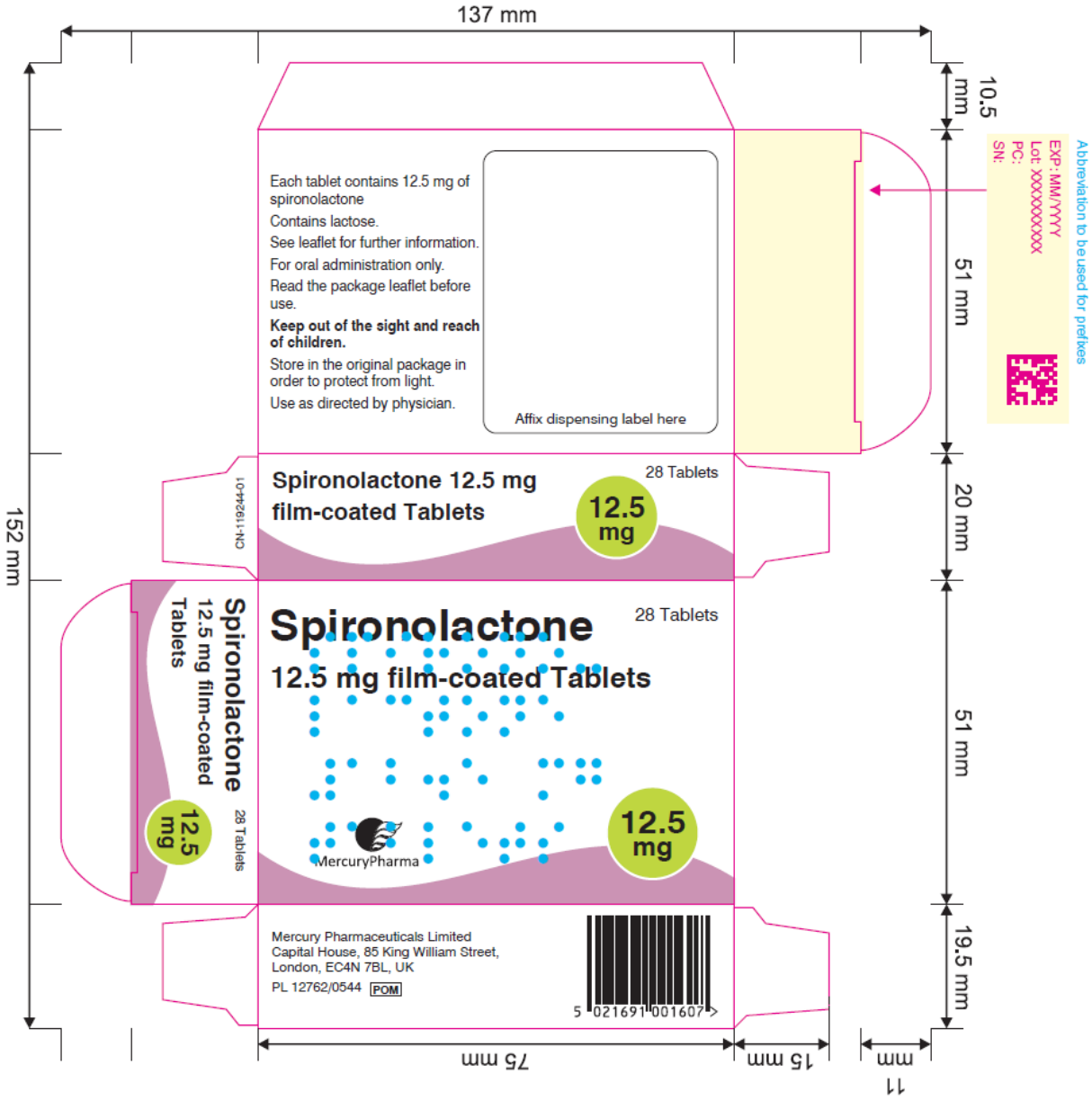
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with spironolactone is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

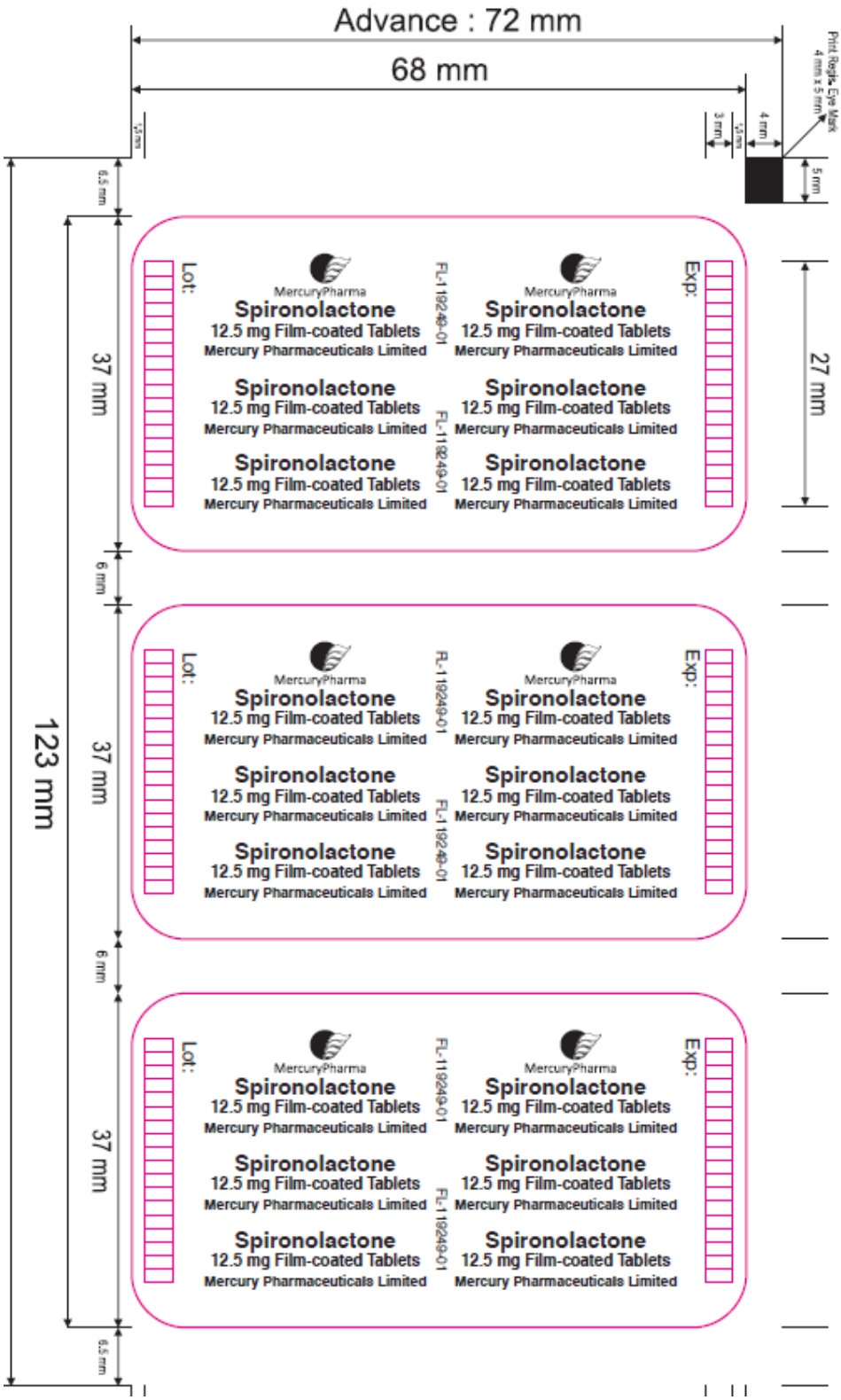
The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.

Spironolactone 12.5 mg Film-coated Tablets

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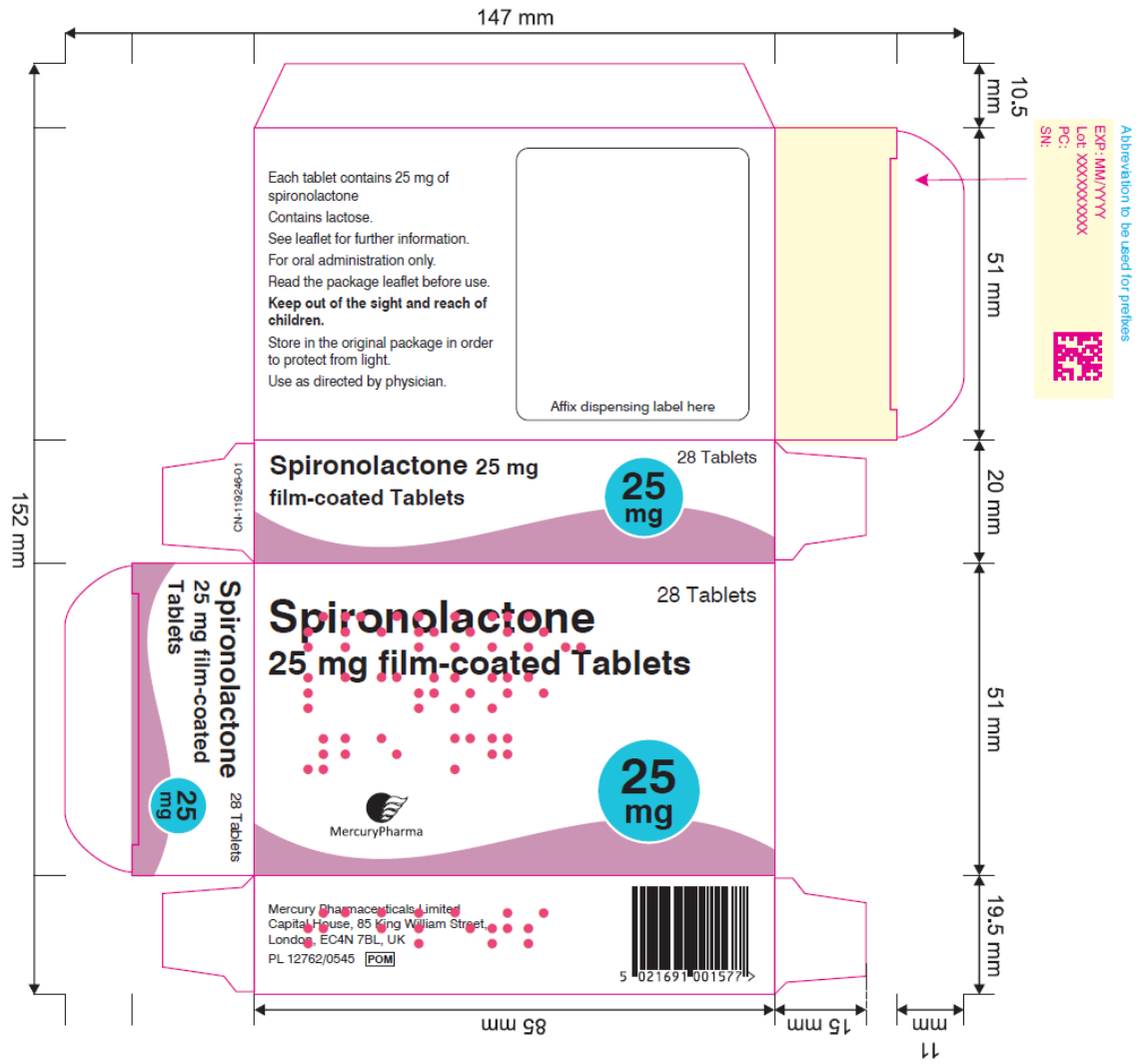
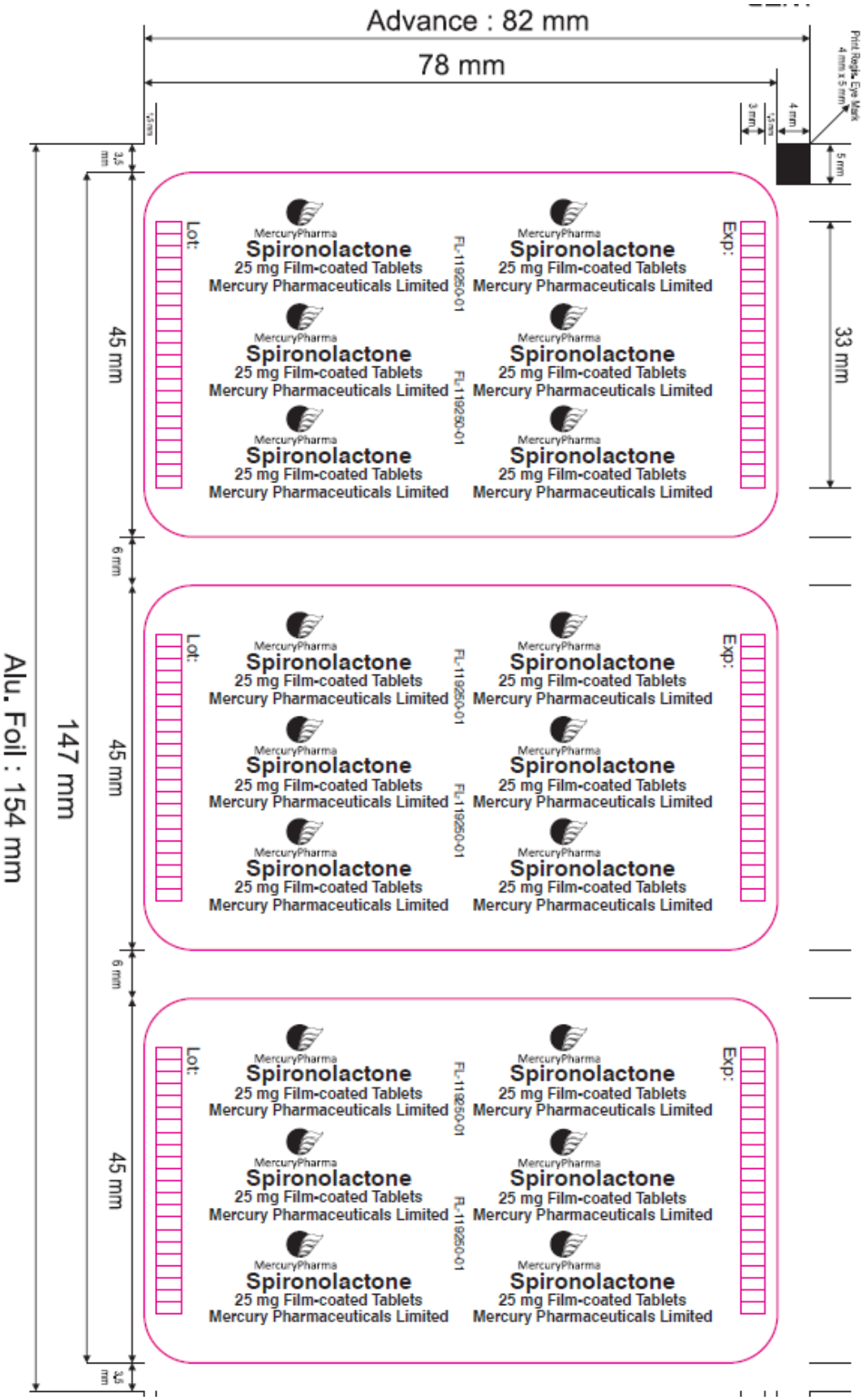
123 mm
27 mm
Lot:
Exp:
MercuryPharma
Spironolactone
12.5 mg Film-coated Tablets
Mercury Pharmaceuticals Limited
FL-11924949-01

Spironolactone 25 mg Film-coated Tablets

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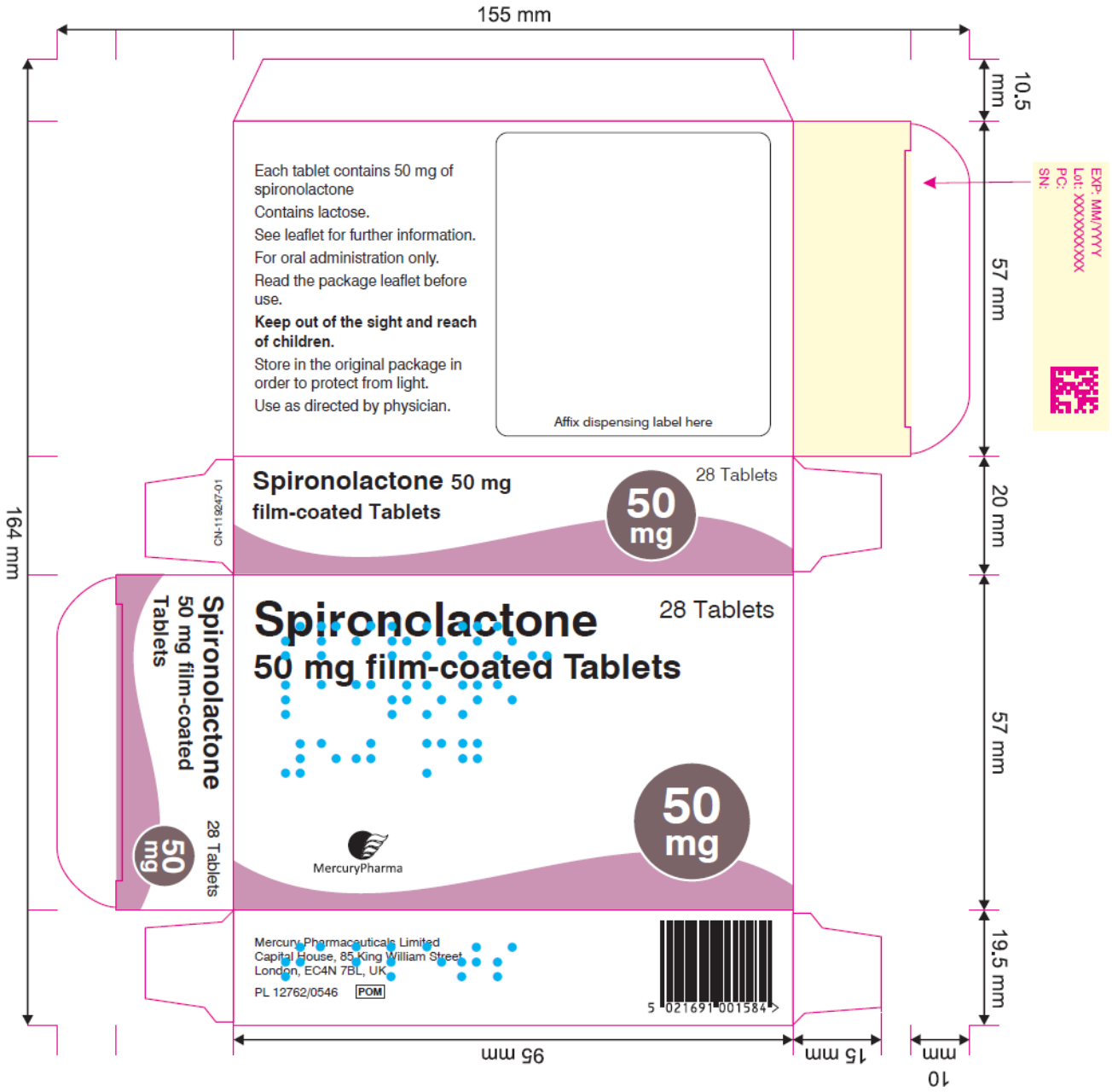
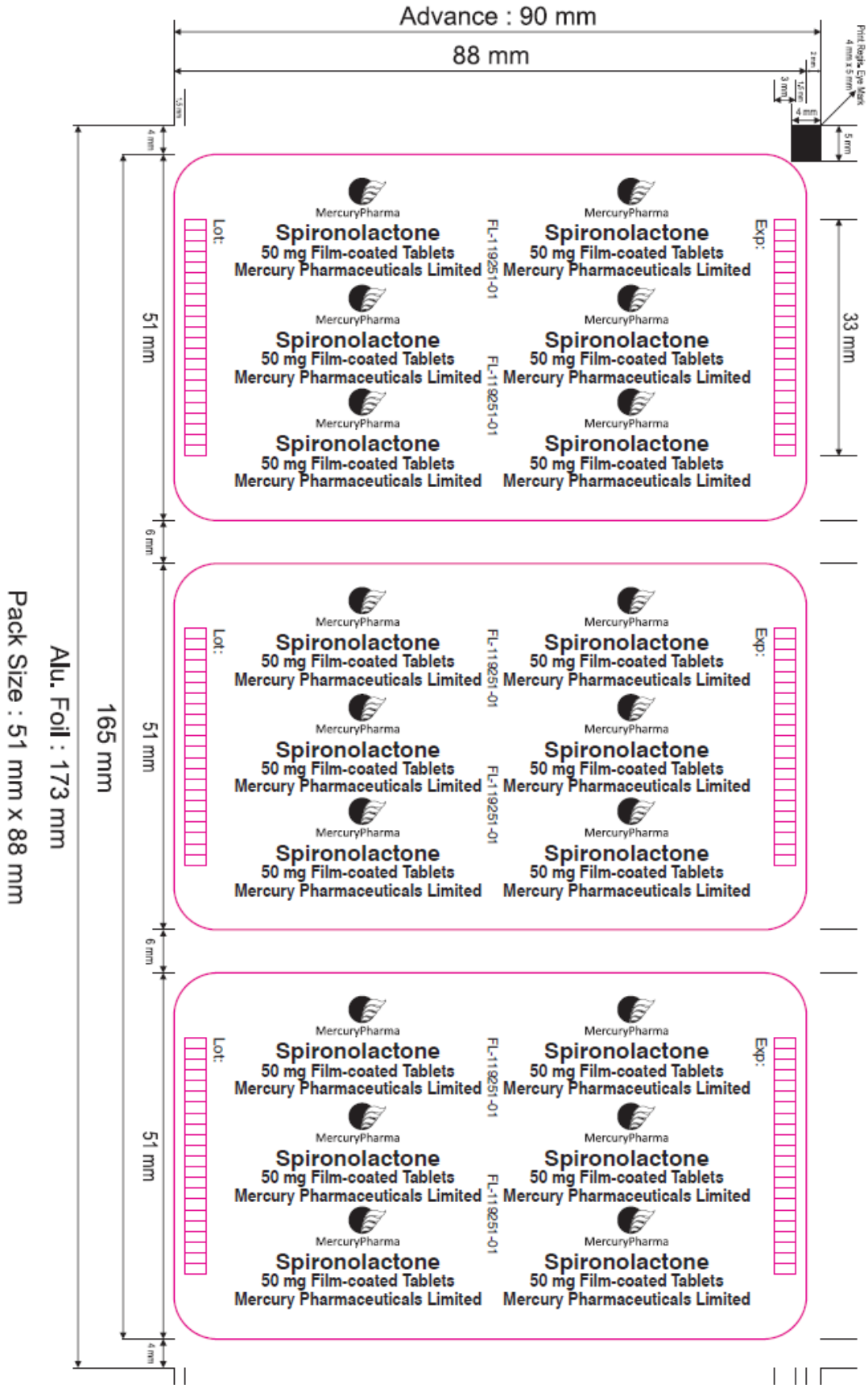
Exp:
MercuryPharma
Spironolactone
25 mg Film-coated Tablets
Mercury Pharmaceuticals Limited
FL-11925O-01

Spironolactone 50 mg Film-coated tablets

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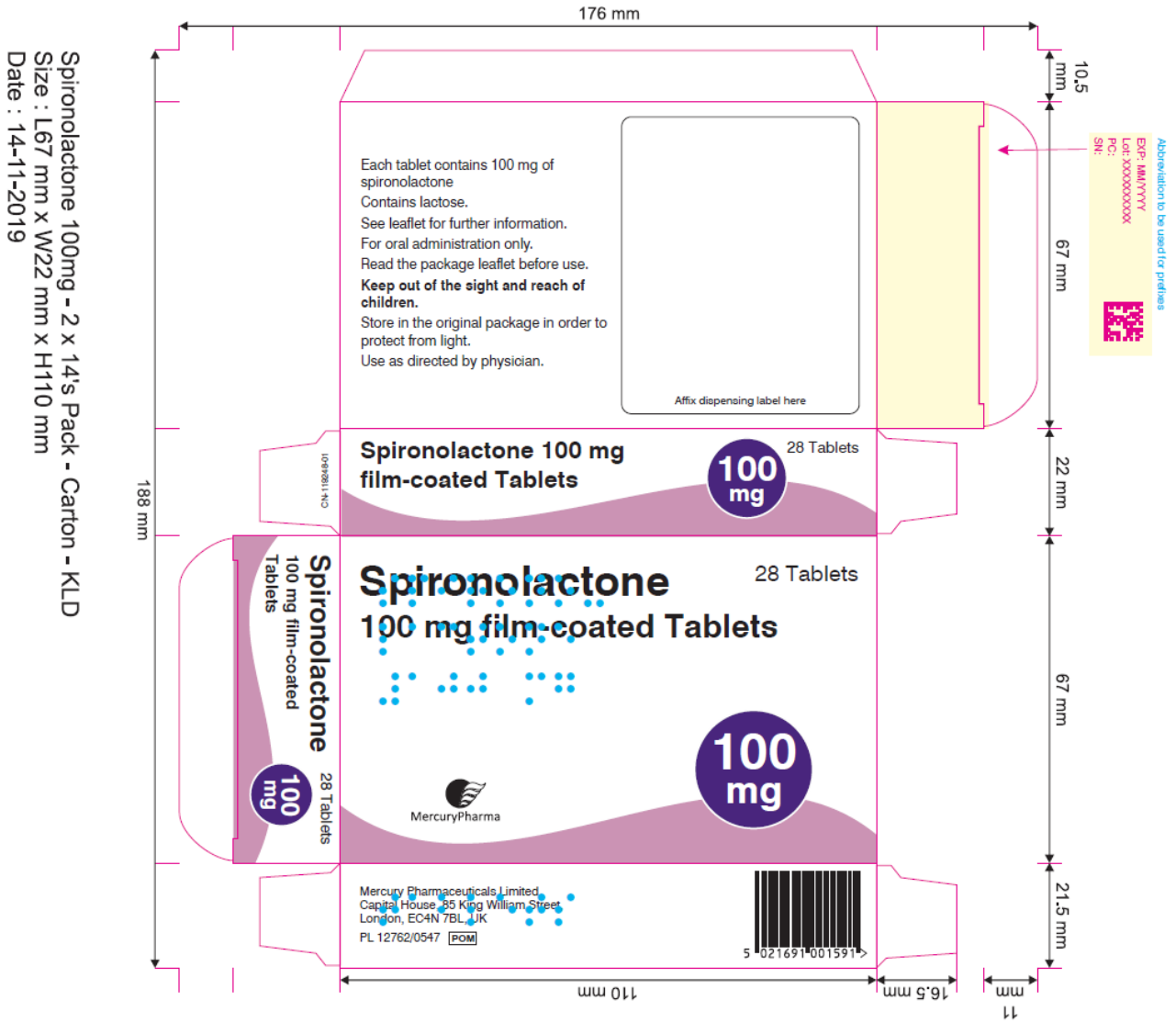
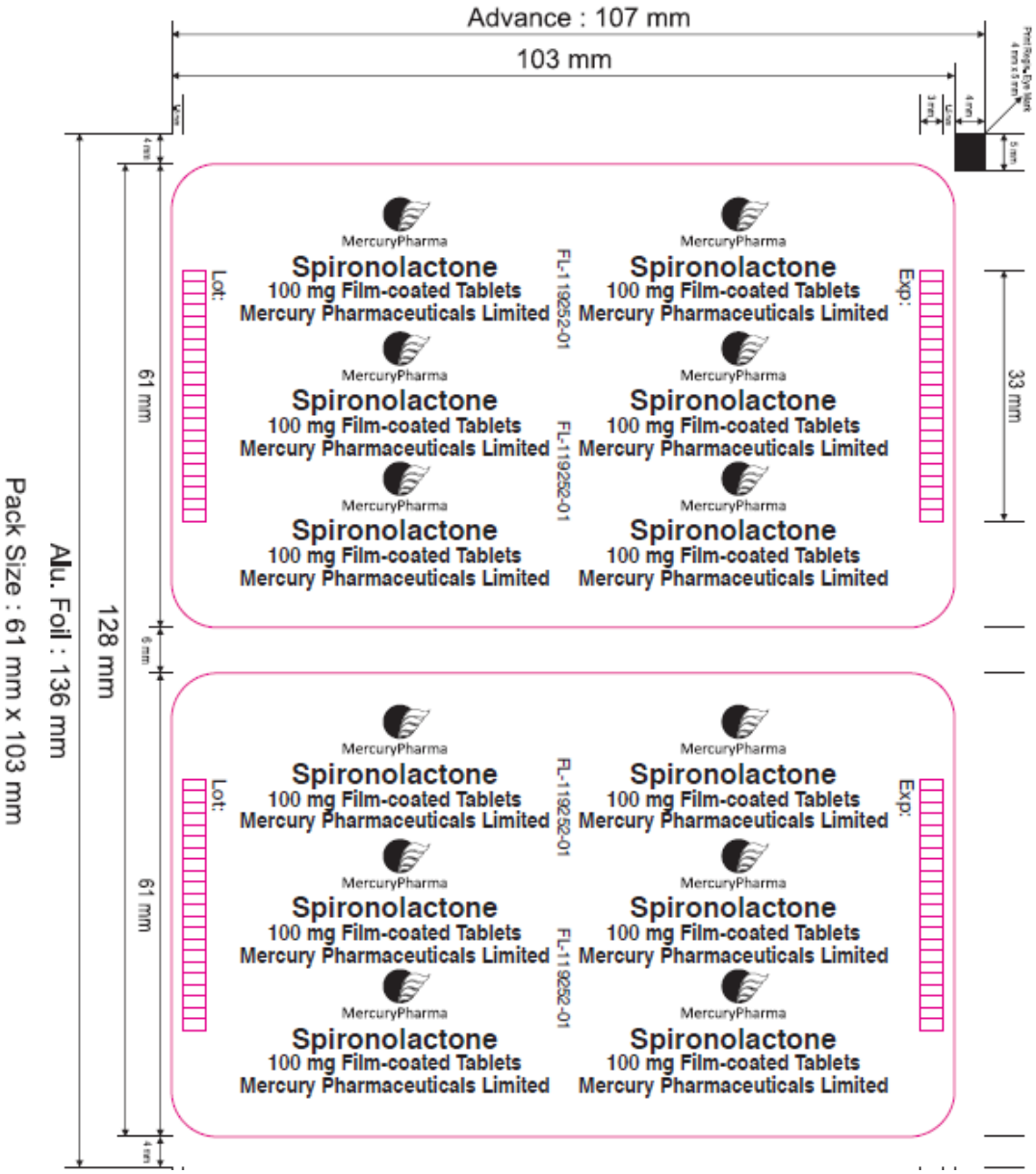
MercuryPharma
Spironolactone
50 mg Film-coated Tablets
Mercury Pharmaceuticals Limited
FL-11925 1-01
FL-11925 1-01
FL-11925 1-01

Spironolactone 100 mg Film-coated tablets

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Exp:
FL-119252-01
MercuryPharma
Spironolactone
100 mg Film-coated Tablets
Mercury Pharmaceuticals Limited

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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