30 March 2023
EMA/175439/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Qaialdo

International non-proprietary name: spironolactone

Procedure No. EMEA/H/C/005535/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADI	Acceptable daily intake
AE	Adverse event
Al / Alu	Aluminium
API	Active pharmaceutical ingredient
AR	Assessment report
ASM	Active substance manufacturer
AUC	Area under the plasma concentration versus time curve
AUC(0-∞)	Area under the plasma concentration versus time curve from zero to infinity
AUC0-t	Area under the plasma concentration time curve from zero to time t
BCS	Biopharmaceutics classification system
BE / BEQ	Bioequivalence
BMI	Body mass index
BSE/TSE	Bovine spongiform encephalopathy / transmissible spongiform encephalopathy
Cave,ss	Average concentration at steady state
CEP	Certificate of suitability
CFR	Code of Federal Regulations
CI	Confidence interval
Cmax	Maximum observed plasma concentration
CoA	Certificate of analysis
CQA	Critical quality attribute
CU	Content uniformity
CV	Coefficient of variation
DAD	diode-array detector
DMF	Drug master file = Active substance master file, ASMF
DPM	Drug product manufacturer
DSC	Differential scanning calorimetry
ECG	Electrocardiogram
EDQM	The European Directorate for the Quality of Medicines & HealthCare
EEA	European Economic Area
EMA	European Medicine Agency
EPAR	European public assessment report
ERA	Environmental risk assessment

FCC	Food Chemical Codex
FDA	Food and Drug Administration
GC	Gas chromatography
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
HDPE	High-density polyethylene
HPLC	High pressure liquid chromatography
HSM	High shear mixer
CHMP	Committee for Human Medicinal Products
ICDD	International Centre for Diffraction Data
ICH	International Conference on Harmonisation
INN	International non-proprietary name
IPC	In-process control
IR	Infrared spectroscopy
IS	internal standard
ISR	incurred sample reanalysis
KF	Karl Fisher
LC/MS/MS	Liquid chromatography coupled with tandem mass spectrometry
LDPE	Low-density polyethylene
LLOQ	Lower limit of quantification
LOD	Loss of drying (1), Limit of Detection (2)
LoQ	List of questions
LOQ	Limit of quantification
MAH	Marketing authorisation holder
MO	Major objection
MS	Mass spectroscopy
N/A	Not applicable
NLT	Not less than
NMR	Nuclear magnetic resonance spectroscopy
NMT	Not more than
OC	Other concern
OGD	Office of generic drugs

PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PI	Principal investigator
PI	Product information
PL	Patient leaflet
PSD	Particle size distribution
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
q.s.	Quantity sufficient
QbD	Quality by design
QC	Quality control
QOS	Quality overall summary
QP	Qualified person
RH	Relative humidity
RRT	Relative retention time
RSD	Relative standard deviation
SAE	Serious adverse event
SD	Standard deviation
SDS	Sodium dodecyl sulfate
SGF	Simulated gastric fluid
SLS	Sodium lauryl sulphate
SmPC	Summary of product characteristics
t½	Terminal half-life
TAMC	Total aerobic microbial count
TLC	Thin liquid chromatography
Tmax	Time to maximum observed concentration
TYMC	Total combined yeasts/moulds count
ULOQ	Upper limit of quantification
UPLC	Ultra high performance liquid chromatography
USP/NF	United States Pharmacopoeia/National formulary
UV	Ultraviolet
XRD	X-Ray diffraction
λz	Terminal elimination rate constant

This is a general list of abbreviations. Not all abbreviations are used in this report.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Nova Laboratories Ireland Limited submitted on 3 November 2021 an application for Marketing authorisation to the European Medicines Agency (EMA) for Qaialdo, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 February 2020. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication.

In the management of refractory oedema associated with congestive cardiac failure; hepatic cirrhosis with ascites and oedema, malignant ascites, nephrotic syndrome, diagnosis and treatment of primary aldosteronism, essential hypertension.

Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available (see sections 5.1 and 5.2).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Aldactone instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Aldactone, 100 mg film-coated tablets
- Marketing authorisation holder: Pfizer Healthcare Ireland
- Date of authorisation: (13-03-1975)
- Marketing authorisation granted by:
  - Member State (EEA): Ireland
    - National procedure
- Marketing authorisation number: PA0822/110/003

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Aldactone

- Marketing authorisation holder: Pfizer Healthcare Ireland
- Date of authorisation: (13-03-1975)
- Marketing authorisation granted by:
  - Member State (EEA): Ireland
    - National procedure
- Marketing authorisation number: PA0822/110/003

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Aldactone 100 mg film-coated tablets
- Marketing authorisation holder: Pfizer Healthcare Ireland
- Date of authorisation: (13-03-1975)
- Marketing authorisation granted by:
  - Member State (EEA): Ireland
    - National procedure
  - Marketing authorisation number(s): PA0822/110/003
- Bioavailability study number(s): INV684 (0207FRM19)

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Frantisek Drafi

The application was received by the EMA on	3 November 2021
The procedure started on	25 November 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 February 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 February 2022
The CHMP Rapporteur circulated Updated CHMP and PRAC Rapporteurs Joint Assessment Report to all CHMP and PRAC members on	17 March 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 March 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	8 September 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	17 October 2022
The PRAC Rapporteur's Updated Assessment Report was circulated to all PRAC and CHMP members on	27 October 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 October 2022
The CHMP Rapporteur circulated Updated CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	3 November 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	10 November 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	17 February 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 March 2023

The CHMP Rapporteur circulated Updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	27 March 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Qaialdo on	30 March 2023

2. Scientific discussion

2.1. Introduction

Heart failure with reduced ejection fraction is initiated when an 'index event' causes the pumping capacity of the heart to be impaired. Reduced pumping capacity of the heart results in compensatory activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system, which together is referred to as 'neurohormonal activation'. Drug therapy of heart failure is based on the use of diuretics, ACE inhibitors, cardiac glycosides, beta blockers, and vasodilators.

Spironolactone is used in the management of oedema associated with excessive aldosterone excretion such as idiopathic oedema and oedema accompanying cirrhosis of the liver, nephrotic syndrome, and heart failure, usually in conjunction with other diuretics. Spironolactone is a useful adjunct to thiazide therapy when diuresis is inadequate or reduction of potassium excretion is necessary.

Spironolactone is used for the short-term preoperative treatment of primary hyperaldosteronism and for long-term maintenance therapy in patients with discrete aldosterone-producing adrenal adenomas who are not candidates for surgery (e.g., adrenalectomy).

This centralised application for a marketing authorisation concerns a hybrid application according to article 10(3) of Directive 2001/83/EC for Qaialdo (spironolactone), 10 mg/ml oral suspension. The application has been submitted by the applicant Nova Laboratoires Ireland Ltd.

The Reference medicinal product is Aldactone 100 mg film-coated tablets (MAA No: PA0822/110/003, Pfizer Healthcare Ireland) authorised since 1975. Compared to the reference medicinal product, Qaialdo has a different pharmaceutical form (oral suspension) and strength. Qaialdo has the same therapeutic indications and route of administration as Aldactone.

One bioequivalence (BE) study has been performed using the reference medicinal product, Aldactone 100 mg, film coated tablets. The test product (oral spironolactone suspension 10 mg/ml, Batch number: NOVg110) and the reference product (Aldactone, Pfizer Healthcare, Ireland), Batch number: NOVPh113, sourced from Ireland) were compared in healthy males and females under fed conditions. (Study No. INV684 (0207FRM19).

Spironolactone is a specific pharmacologic antagonist of aldosterone. It acts primarily through the competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule, where it combines with soluble cytoplasmic aldosterone receptors to form complexes which are inactive and which do not bind to nuclear-acetylated sites, thus preventing a chain of biochemical events leading to the synthesis of physiologically active proteins. Spironolactone causes increased amounts of sodium and water to be excreted, while potassium is retained. Spironolactone acts both as a diuretic and as an antihypertensive drug by this mechanism. The

reduced Na^+ reabsorption caused by spironolactone induces the electrical potential across the tubular epithelium to fall. Qaialdo oral suspension has been developed to substitute for oral tablet formulations of spironolactone, where an oral suspension is clinically beneficial/required to improve acceptability and compliance such as in young children who find swallowing tablets difficult, older patients who prefer liquid medicines and patients with dysphagia. It is presented as a ready to use oral suspension, and hence there is no need for reconstitution or special precautions in preparation of a dose for oral administration. The strength of the proposed liquid formulation of spironolactone is 10 mg in 1 mL.

The posology is the same as that of Aldactone, specifically up to 400 mg/day depending on the indication. Additionally, two dosing syringes are provided for accurate measurement of the prescribed dose of the oral suspension.

Proposed indications

In the management of refractory oedema associated with congestive cardiac failure; hepatic cirrhosis with ascites and oedema, malignant ascites, nephrotic syndrome, diagnosis and treatment of primary aldosteronism, essential hypertension.

Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available (see sections 5.1 and 5.2).

Method of administration

Spironolactone should be taken with meals.

To assist accurate and consistent dose delivery to the stomach, water should be taken after each dose of Spironolactone.

Spironolactone is for oral use and requires redispersing (by shaking the bottle) prior to dosing.

Two dosing syringes (a 1 ml syringe and a 5 ml syringe both graduated in 0.1 ml increments, allowing accurate and reproducible dosing in 1 mg increments) are provided for accurate measurement of the prescribed dose of the oral suspension. It is recommended that the healthcare professional advises the patient or carer which syringe to use to ensure that the correct volume is administered.

In adults without swallowing difficulties, solid oral formulations may be more appropriate and convenient.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as an oral suspension containing 10 mg/ml of spironolactone as active substance.

Other ingredients are: sodium benzoate (E 211), sucrose, sodium citrate (E 331), citric acid monohydrate (E 330), strawberry flavour liquid, masking flavour, polysorbate 80 (E 433), simeticone emulsion 30%, xanthan gum (E 415) and purified water.

The product is available in amber type III glass bottles with tamper evident child-resistant closures (high-density polyethylene (HDPE) with expanded polyethylene liners), as described in section 6.5 of the SmPC. Each pack contains one bottle with 150 mL of oral suspension, a low-density polyethylene

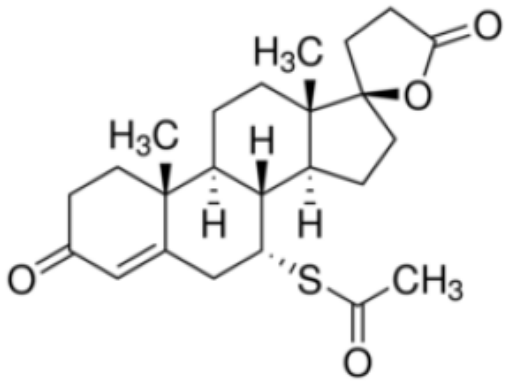
(LDPE) bottle adaptor and 2 dosing syringes (a 1 ml and a 5 ml syringe both graduated in 0.1 ml increments). The oral syringes and bottle adaptor are CE-marked.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of spironolactone is *S*-[(2′*R*)-3,5′-dioxo-3′,4′-dihydro-5′*H*-spiro[androst-4-ene-17,2′-furan]-7α-yl] ethanethioate corresponding to the molecular formula C24H32O4S. It has a relative molecular mass of 416.57 g/mol and the following structure:

Figure 1: Active substance structure



Spironolactone is a white or yellowish-white powder, practically insoluble in water, but soluble in ethanol (96 per cent).

Polymorphism has been observed for spironolactone.

Spironolactone is a BCS Class II drug (low solubility/high permeability). As a result, particle size may influence solubility. The active substance is micronised to achieve a particle size distribution ensuring consistent performance in terms of product homogeneity and dissolution for the finished product oral suspension formulation.

The manufacturer of spironolactone has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for the active substance in regard of compliance with Ph. Eur. monograph 0688, which has been provided within the Marketing Authorisation Application.

2.2.2.2. Manufacture, characterisation and process controls

Spironolactone is supplied from a single manufacturer.

The relevant information has been assessed by EDQM before issuing the CEP.

The container closure system of the active substance (double polyethylene bags placed in cardboard box) is covered by the CEP.

2.2.2.3. Specification(s)

The active substance specification includes the specification and methods of the Ph. Eur. Monograph 0688, additional test in accordance with the CEP (residual solvents) and in-house test for particle size distribution. Tests are: identity, assay, related substances, specific optical rotation, free thiol compounds, loss on drying and sulphated ash (all Ph. Eur.), residual solvents (GC), and particle size distribution (laser diffraction, Ph. Eur.).

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for three commercial batches of active substance were provided. The results were within the specifications and consistent from batch to batch.

The compendial methods and the GC method for residual solvents were evaluated by EDQM in view of the CEP. The particle size distribution method has been adequately validated and described according to ICH Q2.

2.2.2.4. Stability

As prescribed in the CEP, the re-test period of the substance is 5 years if stored in double PE bags, placed in a carboard box.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

The finished product is a white to off-white viscous oral suspension containing 10 mg/ml of spironolactone.

The aim of the product development was:

- To produce a liquid formulation of spironolactone suitable for dosing to children, allowing precise dose adjustment using a graduated oral syringe.
- To produce a chemically and physically stable formulation.
- To ensure a pleasant taste of the formulation which is acceptable to the paediatric population.
- To ensure that the levels of preservatives are adequate but not excessive for paediatric use.
- To provide a pack optimised for the formulation.
- To design a manufacturing process capable of consistently meeting the required quality goals.

The active substance spironolactone shows polymorphism. Data on formulation development studies are adequate.

Spironolactone is known to be bitter tasting, therefore, an effective taste masking system was required in view of palatability for a paediatric population. The palatability of the proposed formulation was also assessed by a questionnaire following ingestion of the oral liquid during the bioequivalence study.

The product development was carried out especially considering the requirements of the paediatric population. The proposed formulation contains no alcohol or colouring agents. No evidence of any

incompatibility between the excipients or between the active substance and the excipients has been found.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards (except flavouring agents/ manufacturer specification and simethicone 30% emulsion/ USP). There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The formulation contains the antimicrobial preservative sodium benzoate. Adequate data on preservative selection, justifying concentration and nature, has been provided. The preservative efficacy studies (in line with Ph. Eur. 5.1.3) along with the stability data demonstrate that the chosen preservative in the respective concentration is effective in preventing microbial growth.

Preservative efficacy was confirmed via stability testing of unopened product, and via in-use testing of product from batches at the beginning and end of the shelf life.

In order to respond to an MO on accuracy of dosing, the applicant has amended the syringe sizes which will be included in the product pack to a 1-mL syringe and a 5-mL syringe, both graduated with 0.1 mL dose increments. This to achieve the necessary dosing accuracy for all intended patients, including those who require very low doses such as neonates.

The discriminatory power of the dissolution method has been demonstrated. The method was found to be discriminatory for changes in sucrose content of the formulation and for changes in the polymorphic form of spironolactone.

The formulation used in the bioequivalence (BE) study is the same as that intended for marketing.

The bioequivalence (BE) study was performed between the proposed product and the reference product Aldactone 100 mg tablets. The results of the study indicate that the test product is equivalent to the reference product with respect to the extent of absorption of spironolactone, but not with respect to the rate of absorption. This might be due to the difference in formulations: the test product is an immediate release oral suspension, while the reference product is a film-coated tablet. Further discussion and conclusion on the clinical relevance of the results of the BE study can be found in the Clinical Pharmacology section of this report.

Comparison of dissolution profiles of reference and test product was not provided, but since the products are not equivalent with respect to the rate of absorption, this is not relevant.

The provided dissolution results for process validation batches, stability batches and the BE batch (all meeting the dissolution acceptance criteria) were considered sufficient to demonstrate consistency and reproducibility of the manufacturing process of this immediate release pharmaceutical form.

The manufacturing process is a standard process which does not involve any novel steps.

The primary packaging is an amber type III glass bottle with tamper evident child-resistant closure (HDPE with expanded polyethylene liner), as described in section 6.5 of the SmPC. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Each pack contains one bottle containing 150 mL of oral suspension, an LDPE bottle adaptor and 2 dosing syringes (a 1 ml and a 5 ml syringe both graduated in 0.1 ml increments). Oral syringes and bottle adaptor are CE-marked. Compliance with EU Regulation 10/2011 is declared both for the oral syringes and for the bottle adaptor. The syringes have been assessed for dose accuracy and precision following the guidance in Ph. Eur. 2.9.27 and EMEA/CHMP/QWP/178621/2004 (Guideline on the suitability of the graduation of delivery devices for liquid dosage forms).

2.2.3.2. Manufacture of the product and process controls

The manufacturing process consists of a series of mixing and homogenisation steps followed by filling into the bottles. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. Process validation on three commercial scale batches demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this manufacturing process of an oral suspension.

2.2.3.3. Product specification(s)

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), pH (Ph. Eur.), viscosity (Ph. Eur.), uniformity of mass (Ph. Eur.), spironolactone content (HPLC/UPLC), identification of spironolactone (HPLC/UPLC, DAD), homogeneity of suspension (HPLC), dissolution (Ph. Eur.), microbial limits (total viable count, Ph. Eur.), and absence of specified micro-organisms (Ph. Eur.).

The set of specification parameters and limits is adequate tests for the proposed pharmaceutical form and are justified based on compendial requirements, relevant CHMP and ICH guidelines, batch release and stability data.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay of active (spironolactone) and preservative (sodium benzoate) and impurities testing has been presented.

Batch analysis results are provided for seven commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The finished product is released on the market based on the above release specifications, through traditional finished product release testing.

2.2.3.4. Stability of the product

Stability data from four commercial scale batches of finished product stored for up to 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Three of these batches were identical to, and the

other batch representative of those proposed for marketing. All four batches were packaged in the primary packaging proposed for marketing.

Samples were tested for appearance, pH, viscosity, spironolactone content, degradation products, sodium benzoate content, homogeneity of suspension, dissolution, microbial limits, and absence of *E. coli*. The analytical procedures used are stability indicating. For three of these batches the stability protocol also included a preservative efficacy test.

No significant changes were observed to any of the measured parameters, even under accelerated conditions.

The preservative efficacy test performed according to Ph. Eur. 5.1.3 demonstrated that the preservative system provides adequate protection from adventitious microbial contamination or proliferation during long-term storage of the unopened product.

Two commercial scale batches were subjected to an in-use stability study: one at the beginning of the shelf life, and one close to the end of the intended shelf-life. The study was conducted over 16 weeks. Bottles were stored at 15-25°C. On each working day the bottle was removed from storage, an aliquot of the suspension was removed using a syringe, then the bottle was returned to storage. This allowed the withdrawal of product on up to 80 occasions from a single bottle of product. All analytical and microbiological parameters remained within specification over the complete study, and preservative efficacy test was confirmed in-use at 12 weeks time-point.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results demonstrate that the product is slightly susceptible to photodegradation, and that the proposed amber glass bottles provide sufficient protection.

Based on available stability data, for unopened product the proposed shelf-life of 2 years without any special storage conditions, and for product after first opening the in-use period of 12 weeks, with storage conditions 'Keep the bottle tightly closed and store below 25°C', as stated in the SmPC (section 6.3 and 6.4), are acceptable.

2.2.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant adequately responded to an MO on dosing accuracy by amending the administration syringes included in the pack. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Pharmacology

2.3.3. Ecotoxicity/environmental risk assessment

No Environmental risk assessment studies were submitted. This was justified by the applicant as the introduction of Qaialdo manufactured by Nova Laboratories Ireland Limited is considered unlikely to result in any significant increase in the combined sales volumes for all spironolactone containing products and the exposure of the environment to the active substance.

2.3.4. Discussion on non-clinical aspects

In view of the data provided, the comprehensive justification for not providing a complete ERA report is accepted.

2.3.5. Conclusion on the non-clinical aspects

The application is acceptable from the non-clinical view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for oral suspension containing spironolactone. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fed conditions.

No formal scientific advice by the CHMP was given for this medicinal product.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of spironolactone based on published literature. The SmPC is in line with the SmPC of the reference product.

GCP aspect

The clinical trials were performed in accordance with GCP as claimed by the applicant.

Tabular overview of clinical studies

To support the application, the applicant has submitted 1 bioequivalence study.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study INV684: Single Centre, Single-Dose, Open-Label, Randomised, Four-Period Crossover Study to assess the Bioequivalence of an Oral Spironolactone Suspension 10 mg/ mL (KayraasTM) and an Oral spironolactone Tablet 100 mg (Aldactone®, Pfizer Healthcare, Ireland) in a Replicate Design in Healthy Males and Females under Fed Conditions

Methods

Methods

- **Study design**

Single-dose, open-label, laboratory-blind, randomised, four period crossover, replicate study with orally administered spironolactone 100 mg conducted under fed conditions in at least 30 healthy males and females at a single study centre.

Table 1: Test and reference products

Reference Product (Treatment A), Dose and Mode of Administration, Batch Number	
Generic name:	Spironolactone
Trade name:	Aldactone®
Manufacturer:	Pfizer Healthcare
Country of origin:	Ireland
Dosage form and strength:	100 mg tablets
Study dose:	100 mg (1 tablet)
Route of administration:	Oral
Packaging number:	NOVPh113
Expiry date:	31 December 2023
Assayed product content:	Not available
Test Product (Treatment B), Dose and Mode of Administration, Batch Number	
Generic name:	Spironolactone
Product Name:	Kayraas™
Manufacturer:	Nova Laboratories Ltd.
Country of origin:	United Kingdom
Dosage form and strength:	Oral Suspension containing 10 mg/mL spironolactone
Study dose:	10 mL of spironolactone 10 mg/mL oral suspension (100 mg)
Route of administration:	Oral

Packaging number:	NOVPh113
Expiry date:	25 May 2021
Assayed product content:	10.1 mg/mL

- **Population(s) studied**

Enrolled and randomised: 36 subjects (18 males and 18 females)

Drop-outs: None

Discontinuers: 1 subject (female)

Completed as per protocol: 35 subjects (18 males and 17 females)

Twenty-nine subjects were Black, 6 were Caucasian, and 1 subject was mixed-race.

Inclusion criteria: Healthy males and females, 18-55 year, BMI 18 - 29 kg/m2, body mass not less than 50 kg, acceptable medical history, vital signs, physical examination, acceptable standard 12-lead ECG and laboratory investigations, non-smokers, males, if not of childbearing potential, females, if not of childbearing potential, of childbearing potential if negative pregnancy test, not lactating, written consent given for participation in the study, willing to consume the meal prescribed before administration of the IMP in full and within the required time.

- **Analytical methods**

The method employed utilised high performance liquid chromatography with tandem mass spectrometry detection (LC-MS/MS). The method was validated at Bioanalytical Services Division, FARMOS (Pty) Ltd prior to sample analysis.

Samples were thawed and assayed in runs where the unknown samples were interspersed with calibration standards (STDs) and quality control (QC) samples, a blank extract (to monitor carry-over) and a zero sample (to monitor interference by the internal standard). The samples of all treatment periods of a particular participant were analysed together in one run. Each run included one standard calibration curve constructed from STDs from at least 6 different concentration levels, ranging from the lower limit of quantification (LLOQ) to the upper limit of quantification (ULOQ), assayed in duplicate. The regression model that was determined and used during the method validation was applied. Quality control samples were assayed in duplicate using at least 3 different concentration levels (one at ~ 3 x LLOQ [QClow], one QC at mid-range (~ 50% of the ULOQ [QCmedium]) and one within ~ 20 - 25% of the ULOQ [QChigh]), or at least 5% of the number of study samples, whichever was higher.

The parent analyte (spironolactone) and active metabolites (7α thiomethyl spironolactone, 6β hydroxy 7α thiomethyl spironolactone and canrenone) were measured, however bioequivalence assessment was conducted only on the parent spironolactone.

The bioanalytical method was calibrated over the range 3.13 – 400 ng/ml.

Internal standard for spironolactone determination was SPIR-d7. Certificates of analysis were submitted.

- **Pharmacokinetic Variables**

Primary pharmacokinetic variables were Cmax and AUC(0-t).

Secondary pharmacokinetic variables were AUC(0-∞), tmax, λz, t½

- **Statistical methods**

The test product was compared to the reference product by means of statistical analysis with respect to the primary PK parameters for spironolactone using ANOVA with sequence, subject(sequence), product and period effects after logarithmic transformation of the data. Upon antilog transformation of the difference estimates of "test – reference" the geometric means ratio of the test and reference product ("test/reference"), as well as the corresponding 90% confidence interval (CI) for the geometric mean ratio of the test and reference products ("test/reference") and the intra-subject Coefficient of variation percentage (CV%) were provided.

Bioequivalence of the test and reference products was assessed on the basis of the 90% CIs for estimates of the geometric mean ratios between the primary PK parameters for spironolactone in relation to the conventional acceptance range of 70.00% to 143.00% for Cmax and 80.00% to 125.00% for AUC(0-t).

In addition, for exploratory purposes, the intra-subject (within-subject) variability between treatment periods were analysed separately for both the test and reference products. This variation was expressed with CV% derived from a similar model used to test for bioequivalence but selecting only data for one product at a time.

All AUCs were calculated using the linear trapezoidal rule.

Results

Based on previously conducted PK and bioequivalence studies which demonstrated high (>30% CV) intra-subject variability in Cmax, spironolactone was assumed to be a highly variable drug. Hence, bioequivalence of the test and reference products was assessed on the basis of the 90% confidence

intervals (CIs) for estimates of the geometric mean ratios between the primary PK parameters for spironolactone in relation to the conventional acceptance range of 70.00% to 143.00% for Cmax and 80.00% to 125.00% for AUC(0-t) following the guidance on bioequivalence (CPMP/EWP/QWP/1401/98 rev.1) in relation to high variable drug products.

Table 2: Summary of plasma PK parameters for Spironolactone (INV684)

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test product	Reference Product
$AUC_{(0-t)}$ (h*ng/mL)	464.6 (224.7)	451.7 (222.6)
$AUC_{(0-\infty)}$ (h*ng/mL)	505.2 (238.3)	496.8 (239.6)
Cmax (ng/mL)	160.7 (82.66)	242.2 (122.3)
Tmax[1] (h)	0.750 (0.25, 2.33)	1.250 (0.50, 5.00)
$T_{1/2,z}$ (h)	5.23 (2.17)	4.60 (2.66)

[1] Median (Min, Max)

Table 3: Summary of statistical analysis of plasma spironolactone primary pharmacokinetics

			LS Means		Test / Reference Geometric Mean Ratio (%)		
Parameter (Unit)	n / N (Test)	n / N (Reference)	Treatment B (Test)	Treatment A (Reference)	Estimate	90% CI	Model Intra CV%
C_{max} (ng/mL)	72 / 36	71 / 36	142.24	215.03	66.15	(61.62 ; 71.01)	25.95
AUC_{0-t} (h*ng/mL)	72 / 36	71 / 36	417.56	411.36	101.51	(98.11 ; 105.02)	12.30

Table 4: Intra-CV percentage between periods for spironolactone

Product	Parameter (Unit)	Model Intra CV%
Treatment A to Treatment A	C_{max} (ng/mL)	24.65
	AUC_{0-t} (h*ng/mL)	10.91
	$AUC_{0-\infty}$ (h*ng/mL)	10.85
Treatment B to Treatment B	C_{max} (ng/mL)	19.92
	AUC_{0-t} (h*ng/mL)	12.94
	$AUC_{0-\infty}$ (h*ng/mL)	13.21

CV% = coefficient of variation percentage
Treatment A (reference): Aldactone® 100 mg tablet
Treatment B (test): Kayraas™ 10 mL oral suspension

The intra-subject variability in Cmax was below the threshold for classification as a highly variable drug (<30% CV). Based on previously conducted PK and bioequivalence studies which demonstrated high (>30% CV) intra-subject variability in Cmax, the applicant assumed spironolactone to be a highly variable drug. It is likely that, unlike the previous studies, the replicate study design employed in the current investigation has allowed the intra-subject variability to be determined with greater precision.

Palatability

As part of the bioequivalence study described above, the palatability (taste, aftertaste, smell, texture, ease of use) of the test IMP was assessed by questionnaire following ingestion of the oral liquid. The questionnaire comprised of five questions with either yes/no or visual analogue scale (VAS) responses required. The VAS responses were captured as lengths in mm (out of a maximum of 100 mm).

Table 5: Summary of taste evaluation and palatability results

Category (Unit)	Sequence ABAB (N=18)	Sequence BABA (N=18)	Overall (N=36)
Taste (mm)			
n	18	18	36
Mean	59.3	67.9	63.6
SD	24.10	24.77	24.47
Min	22	8	8
Median	62.5	74.5	69.5
Max	99	99	99
Smell (mm)			
n	18	18	36
Mean	67.4	77.4	72.4
SD	16.55	18.09	17.82
Min	39	50	39
Median	70.0	76.5	75.0
Max	95	99	99
Texture (mm)			
n	18	18	36
Mean	71.0	68.4	69.7
SD	16.50	26.18	21.61
Min	38	8	8
Median	75.0	73.5	75.0
Max	97	99	99
Ease of Use (mm)			
n	18	18	36
Mean	71.3	70.4	70.8
SD	20.83	24.13	22.22
Min	25	12	12
Median	75.5	73.5	74.5
Max	99	99	99

N = number of subjects; n = number of subjects who reported palatability results; SD = standard deviation
Treatment A (reference): Aldactone® 100 mg tablet
Treatment B (test): Kayraas™ 10 mL oral suspension
Taste assessment was conducted after the second administration of the test product using a 100 mm VAS.
Results are irrelevant to the reference product, and per sequence summaries are only shown for exploratory purposes.

Additional pharmacokinetic data

To justify that the differences seen in Cmax do not have a clinically relevant impact, the applicant submitted further PK analyses, specifically comparison of Cmin and estimated average concentration at steady state between test and reference product.

Although Cmin is not included in the bioequivalence criteria the mean concentrations at 12 hours (in the case of twice daily dosing) and 24 hours (once daily dosing) of spironolactone and the active metabolites (7α-thiomethyl-spironolactone, 6β- hydroxy-7α-thiomethyl-spironolactone and canrenone) are very similar following dosing with Aldactone and Spironolactone 10mg/ml oral suspension.

Table 6: Mean Cmin values for the tablet and liquid

	Cmin, 12h (ng/ml)		Cmin, 24h(ng/ml)	
	Aldactone	Spironolactone 10mg/ml oral suspension	Aldactone	Spironolactone 10mg/ml oral suspension
Spironolactone	7.304	7.560	4.803	4.551
7α-thiomethyl-spironolactone	62.07	65.23	38.77	40.03
6β-hydroxy-7α-thiomethyl-spironolactone	53.76	54.47	33.13	33.97
Canrenone	45.63	46.72	31.39	31.69

Values are geometric means. Extracted from Table 14.2.1.1

The average concentration at steady state is a calculation of the total exposure over 1 dosing interval (i.e. AUC0-τ) divided by the time of the dosing interval. While concentrations rise and fall during a dosing interval at steady state, the Cave,ss does not change. The factors that control Cave,ss are the dose, the dosing interval, and the clearance. Thus, for the same Spironolactone 10 mg/mL oral suspension / Aldactone dose and dosing interval, and assuming clearance is the same for both formulations (since AUC estimates are the same), Cave,ss concentrations for both formulations will be the same. Lower doses and longer intervals will result in lower Cave,ss values, while higher doses and shorter intervals will give higher Cave,ss values. It should therefore be reassuring that the Cave,ss are essentially the same for the two formulations (Table 7).

Table 7: Estimated Steady state parameters

	AUC (0-τ) h.ng/ml*		Cave,ss** ng/ml	
	Aldactone	Spironolactone 10 mg/mL oral suspension	Aldactone	Spironolactone 10 mg/mL oral suspension
Spironolactone	451	456	18.8	19.0
7α-thiomethyl-spironolactone	3328	3305	138.7	137.7
6β-hydroxy-7α-thiomethyl-spironolactone	2531	2310	105.5	96.3
Canrenone	2467	2485	102.8	103.5

Values are geometric means. Data extracted from 14.2.1.2.
**AUC within a 24hour dosing interval at steady state. Assuming $AUC_{(0-\infty)}$ after a single dose is equivalent to AUC within a dosing a dosing interval at steady state, $AUC_{0-\tau}$.*
***50mg dose administered at 24 hour intervals*

- **Safety data**

No deaths or SAEs were reported during the study, and no AE was of severe intensity. One subject presenting with iron deficiency anaemia was withdrawn from the study prior to Treatment Period 4. The investigator regarded this AE as unlikely related to the IMP. Fourteen of the 36 subjects reported 27 AEs. Ten of the events were considered by the investigator as possibly related to the IMP. Of these, 2 events were considered of moderate intensity and 8 as mild in intensity. The most common IMP-related AEs were headache (3 events experienced 3 by subjects) and somnolence (2 events experienced by 1 subject on 2 separate occasions), and all were mild in intensity. Other IMP related

AEs included single events of dry eye (mild), eye pruritus (mild), nausea (moderate), vomiting (moderate) and hyperkalaemia (mild).

Post-hoc population pharmacokinetics (popPK) modelling and analysis

Based on the bioequivalence study, Qaialdo (Test, oral suspension) was shown to be bioequivalent to Aldactone (Reference, tablet) after single dosing with respect to total exposure (AUC0-t), but not with respect to Cmax. Mean Cmax for Qaialdo was 34% lower as compared to Cmax for Aldactone (point estimate 0.66; 90% CI 0.62-0.71), after single dosing.

To address the concentration-time profiles at steady-state for spironolactone, the applicant has conducted a post-hoc population pharmacokinetics (popPK) modelling and analysis.

Individual exposure variables of spironolactone and TMS at steady-state, namely AUC(0-tau)ss and Cmax,ss, were calculated using the developed PK model following once and twice daily dosing for 10 days. Boxplots of simulated spironolactone and TMS AUC(0- tau)ss and Cmax,ss values are shown in Figure 2 - Figure 5 below, and are summarised in Table 8 - Table 11.

Table 8: Simulated spironolactone AU (0-tau)ss

Formulation	QD/ BID	5th perc. [h·ng/mL]	95th perc. [h·ng/mL]	Median [h·ng/mL]	Arith. Mean [h·ng/mL]	Arith. SD [h·ng/mL]	Geo. Mean [h·ng/mL]
Aldactone	QD	240	893	462	501	215	461
Qaialdo	QD	240	893	462	501	215	461
Aldactone	BID	120	447	231	251	108	230
Qaialdo	BID	120	447	231	251	108	230

QD,quaque die (one a day); BID, bis in die (twice a day); perc., percentile; Arith., arithmetic; Geo., geometric; SD, standard deviation.

Table 9: Simulated TMS AUC (0-tau)ss

Formulation	QD/ BID	5th perc. [h·ng/mL]	95th perc. [h·ng/mL]	Median [h·ng/mL]	Arith. Mean [h·ng/mL]	Arith. SD [h·ng/mL]	Geo. Mean [h·ng/mL]
Aldactone	QD	1493	7537	3302	3752	2007	3318
Qaialdo	QD	1493	7537	3302	3752	2007	3318
Aldactone	BID	746	3767	1651	1876	1002	1659
Qaialdo	BID	746	3767	1651	1876	1002	1659

QD,quaque die (one a day); BID, bis in die (twice a day); perc., percentile; Arith., arithmetic; Geo., geometric; SD, standard deviation.

Table 10: Simulated spironolactone Cmax, ss

Formulation	QD/ BID	5th perc. [ng/mL]	95th perc. [ng/mL]	Median [ng/mL]	Arith. Mean [ng/mL]	Arith. SD [ng/mL]	Geo. Mean [ng/mL]
Aldactone	QD	75.6	270	147	155	59.2	144
Qaialdo	QD	55.5	211	112	118	47.6	109
Aldactone	BID	41.6	138	76.3	81.1	30.1	75.8
Qaialdo	BID	31.3	112	59.2	63.1	24.2	58.8

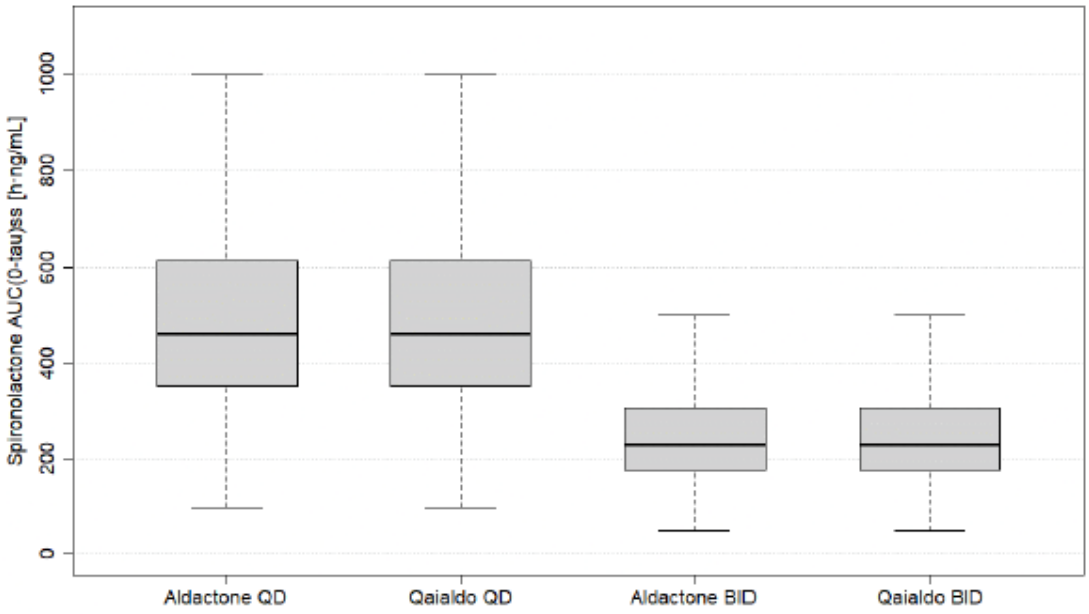
QD,quaque die (one a day); BID, bis in die (twice a day); perc., percentile; Arith., arithmetic; Geo., geometric; SD, standard deviation.

Table 11: Simulated TMS Cmax,ss

Formulation	QD/ BID	5th perc. [ng/mL]	95th perc. [ng/mL]	Median [ng/mL]	Arith. Mean [ng/mL]	Arith. SD [ng/mL]	Geo. Mean [ng/mL]
Aldactone	QD	205	780	449	470	181	434
Qaialdo	QD	164	612	346	369	144	340
Aldactone	BID	129	505	279	296	119	273
Qaialdo	BID	108	428	232	247	104	227

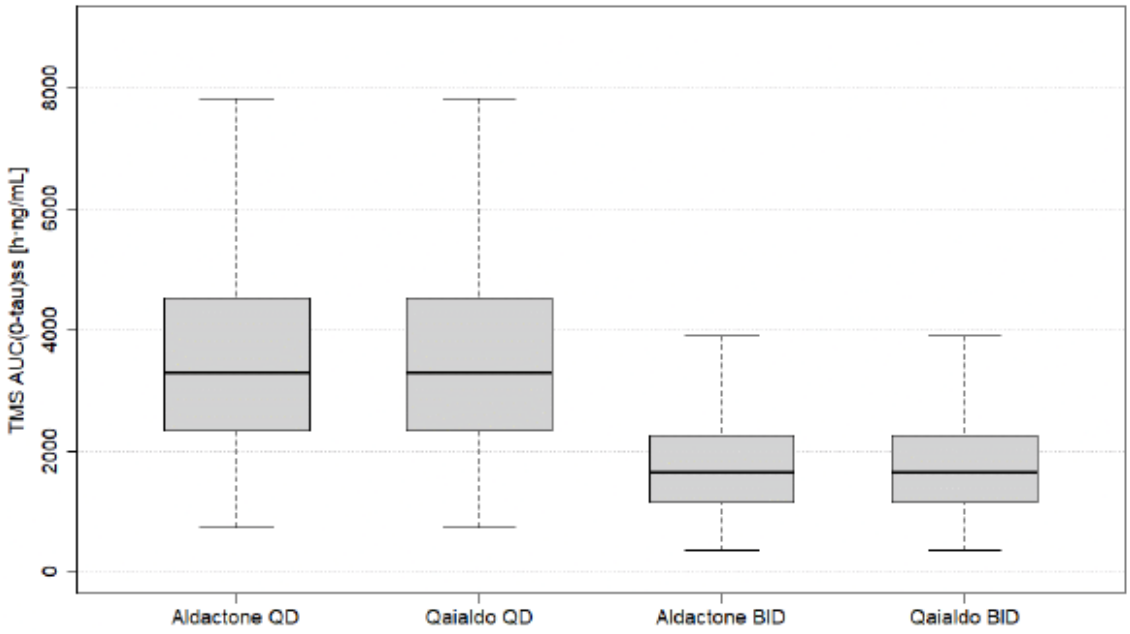
TMS, 7α-thiomethyl-spironolactone; QD,quaque die (one a day); BID, bis in die (twice a day); perc., percentile; Arith., arithmetic; Geo., geometric; SD, standard deviation.

Figure 2: Box plot of model predicted spironolactone AUC (0-tau)ss stratified by dosing regimen



Each box covers the interquartile range (IQR) of all simulated values. The medians are represented by bold, horizontal black lines and whiskers extend to 1.5 times the IQR.

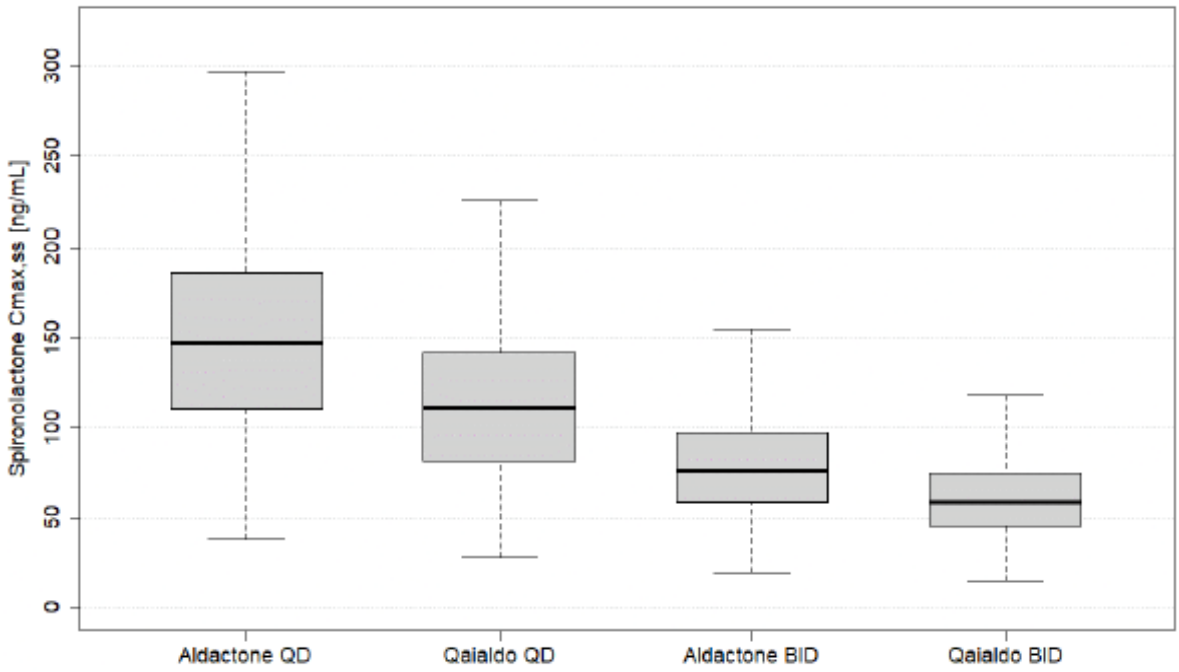
Figure 3: Box plot of model predicted TMS AUC (0-tau)ss stratified by dosing regimen



TMS, 7α-thiomethyl-spironolactone

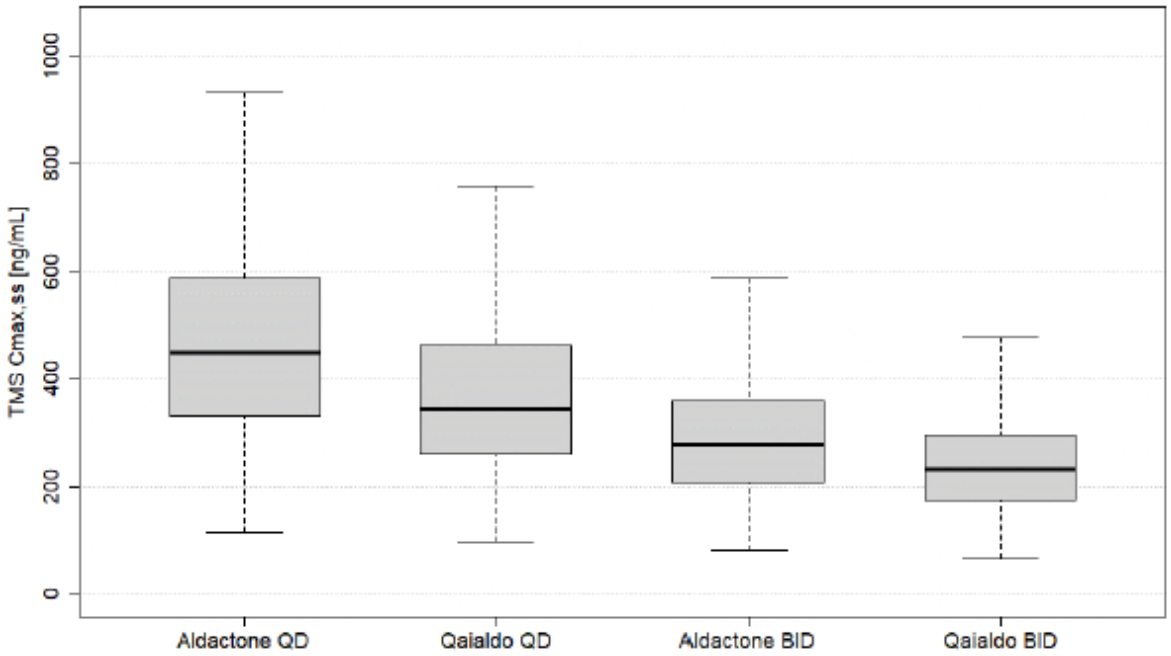
Each box covers the interquartile range (IQR) of all simulated values. The medians are represented by bold, horizontal black lines and whiskers extend to 1.5 times the IQR.

Figure 4: Box plot of model predicted spironolactone Cmx,ss stratified by dosing regimen



Each box covers the interquartile range (IQR) of all simulated values. The medians are represented by bold, horizontal black lines and whiskers extend to 1.5 times the IQR.

Figure 5: Box plot of model predicted TMS Cmax, ss stratified by dosing regimen



TMS, 7α-thiomethyl-spironolactone.

Each box covers the interquartile range (IQR) of all simulated values. The medians are represented by bold, horizontal black lines and whiskers extend to 1.5 times the IQR.

Third, steady-state concentration-time profiles after 10 days of dosing were visualised for each dosing regimen (Figure 6 - Figure 9). The median and the range from the 5th to the 95th percentile of the simulated data are shown as the solid red line and pink shaded region, respectively.

Figure 6: Spironolactone – time profile following Aldactone and Qaialdo, BID dosing

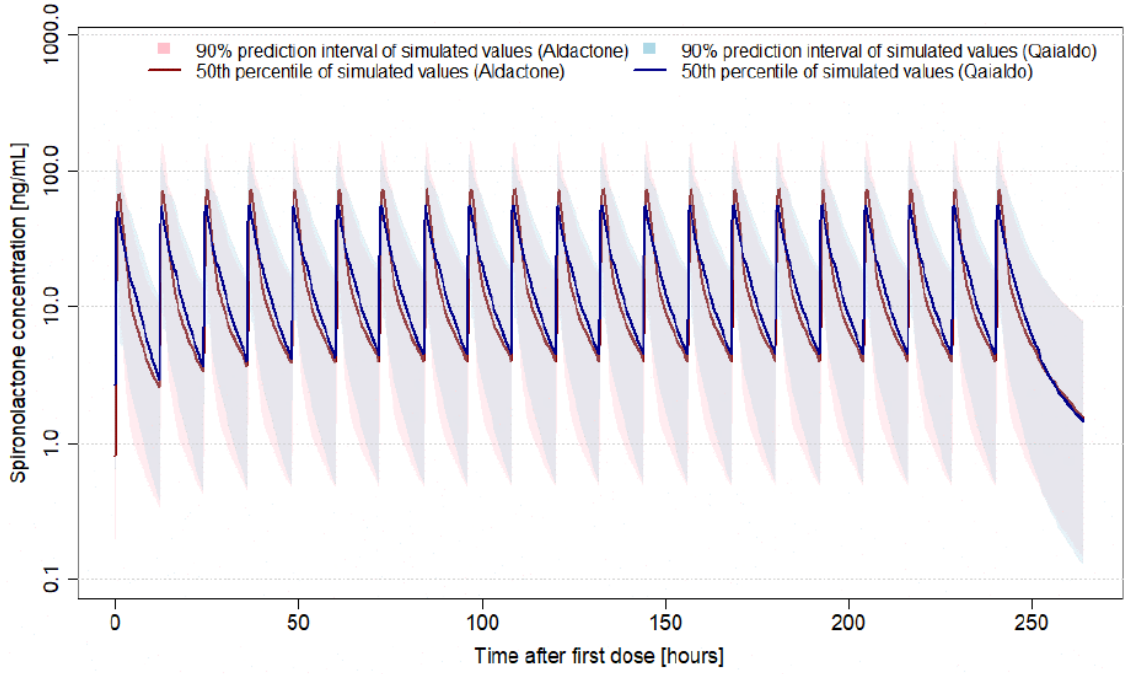


Figure 7: Spironolactone – time profile following Aldactone and Qaialdo, QD dosing

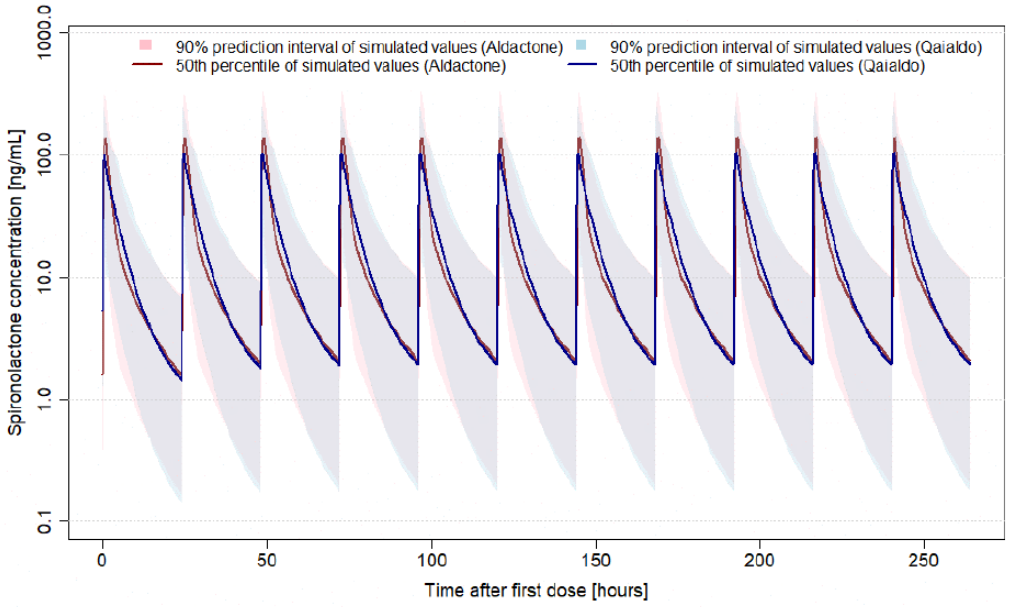


Figure 8: TMS time profile following Aldactone and Qaialdo, BID dosing

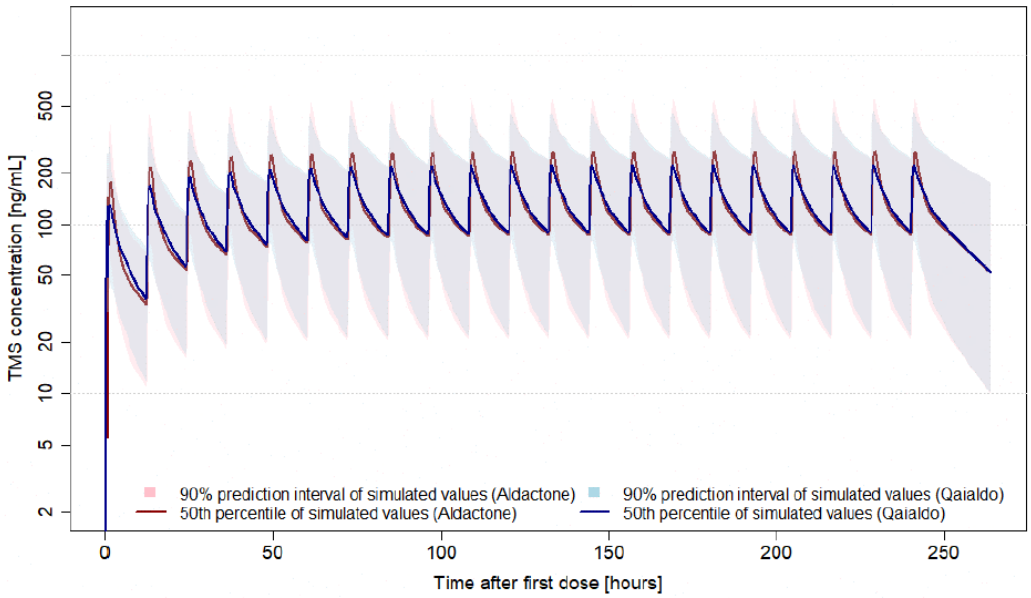
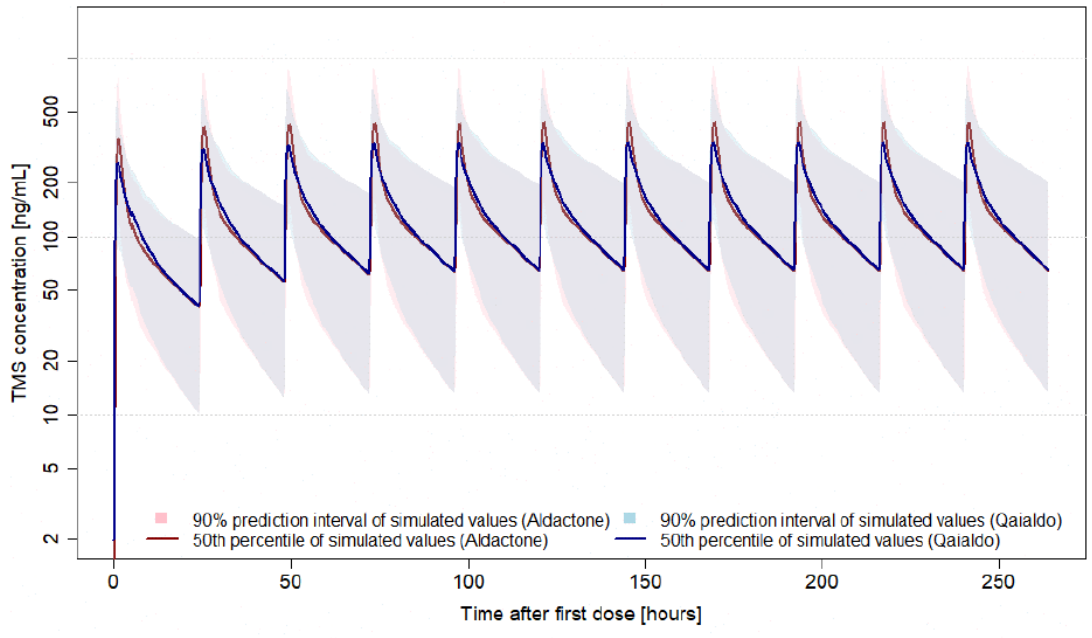


Figure 9: TMS time profile following Aldactone and Qaialdo, QD dosing



Results

The assumption of linear pharmacokinetics is acceptable, and the population PK model appears fit-for-purpose. The VPC plots, stratified by formulation, indicated that the popPK model is able to explain the central tendency well and overall variability of the observed PK data adequately.

The simulations show that total daily exposure for both regimens at steady state remains the same between both products, as is to be expected. Furthermore, the simulations show that mean Cmax for Qaialdo is 24% lower as compared to Aldactone after once daily dosing, and 22% lower after BID dosing.

Although Cmin,ss was not calculated and had to be derived from the C-t plots, it seems to be similar for once daily and twice daily dosing for both products.

Since the approved posology states that the dose can be divided for administration every 12h or 24h, it is clear that the efficacy is mainly driven by the total exposure (i.e. Cave,ss) and not by the shape of the curve (thus Cmin,ss and Cmax,ss).

Therefore, it may be expected that the differences of approximately 20% in Cmax and Cmin at steady state between Qaialdo and Aldactone have no clinically relevant effect at steady state dosing.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.3. Discussion on clinical pharmacology

This is an application for a hybrid medicinal product containing spironolactone. The reference medicinal product is Aldactone, the two products differ in pharmaceutical form (oral solution vs. film-coated tablet). To support this application, the applicant submitted a review of pre-clinical and clinical data as well as one bioequivalence study comparing Aldactone to Qaialdo. The study was a single-dose, open-label, laboratory-blind, randomised, four period crossover, replicate study with orally administered spironolactone 100 mg conducted under fed conditions in at least 30 healthy males and females at a single study center. Based on previously conducted PK and bioequivalence studies which demonstrated high (>30% CV) intra-subject variability in Cmax, the applicant assumed spironolactone to be a highly variable drug. Hence, a modified acceptance range for the 90% confidence interval was proposed: 70.00% - 143.00% for Cmax and 80.00% - 125.00% for AUC(0-t). The 90% CIs for AUC(0-t) were within the predefined bioequivalence limits (CI: 98% - 105%). However, the lower value of the 90% CIs for the Cmax extended below the predefined bioequivalence limit of 70.00% (CI: 62% - 71%). The lack of bioequivalence as shown with Cmax falling outside the already extended range was a major issue.

The presented bioequivalence study did not demonstrate that spironolactone is a highly variable drug. The extended range of 70.00% to 143.00% CI for Cmax cannot be justified based on the results from the bioequivalence study, as the model CV between periods was for Cmax 24.65 % and 19.92 %. The extent of the widening should be defined based upon the within-subject variability seen in the bioequivalence study using scaled-average-bioequivalence (see CPMP/EWP/QWP/1401/98 Rev.1). The extended range of 70.00% to 143.00% CI for Cmax is therefore not acceptable.

The applicant was expected to provide a proof that the absence of comparable bioavailability between Qaialdo and Aldactone in Cmax will not have an impact on the pharmacodynamic response with focus of discussion on Cmin and steady state concentration. The applicant has explained the differences in Cmax between Aldactone and Qaialdo by a different solubility. Additionally, it has been pointed out that the 12 h and 24 h Cmin after single dose administration is very similar between Aldactone and Qaialdo. The applicant also claims that based on the terminal half-life of spironolactone (4-5 h), significant accumulation of the drug is unlikely after a single administration. Further, the applicant states that with regard to the correlation of pharmacokinetics and pharmacodynamic response,

average concentration at steady state (Cave,ss) is more important and shows that Cave,ss is similar between Aldactone and Qaialdo. These parameters are however only estimated by the applicant from AUC0-tau after a single dose. This approach is considered to be imprecise and may not correspond to the reality. The applicant also argues the fact that since spironolactone has a slow onset of action, a mere difference in Cmax is unlikely to affect the pharmacodynamic response. Lastly, spironolactone is a prodrug, which is metabolised to 3 metabolites, for which the estimated Cave,ss and AUC0-τ values were also similar between the two formulations. In conclusion, the justification of absence of Cmax bioequivalence with an estimated Cave,ss was not accepted by CHMP due to reasons described above. The applicant was further asked to justify that the absence of comparability between Qaialdo and Aldactone in concentration-time (C-t) profile of spironolactone will not negatively affect the pharmacodynamic response to spironolactone.

The applicant stated that Cave,ss is considered more important for the pharmacological effect than Cmax,ss or Cmin,ss. However, C-t profiles of spironolactone and its active metabolites for the oral tablet and suspension formulation under steady-state condition, using the single dose data and the superposition principle assuming linear pharmacokinetics, were not provided. This was required to be submitted for at least once-daily and twice-daily dosing, since spironolactone can be taken either as a single daily dose but also in divided doses.

To further substantiate the statement of the applicant that Cave,ss is considered most important for the pharmacological effect, exposure-response relationships or impact of the posology allowing the daily dosage to be given at various divided doses on exposure-response relationships was requested to be discussed.

To address the concentration-time profiles at steady-state for spironolactone, the applicant has conducted a post-hoc population pharmacokinetics (popPK) modelling and analysis. The assumption of linear pharmacokinetics is acceptable, and the population PK model appears fit-for-purpose as well given that simple superposition principle would also have been sufficient. The visual predictive checks (VPC) plots, stratified by formulation, indicate that the popPK model is able to explain the central tendency well and overall variability of the observed PK data adequately.

The simulations show that total daily exposure for both regimens at steady state remains the same between both products. Furthermore, the simulations show that mean Cmax for Qaialdo is 24% lower as compared to Aldactone after once daily dosing, and 22% lower after BID dosing.
Although Cmin,ss was not calculated and had to be derived from the C-t plots, it seems to be similar for once daily and twice daily dosing for both products.

Since the approved posology states that the dose can be divided for administration every 12h or 24h, it is clear that the efficacy is mainly driven by the total exposure (i.e. Cave,ss) and not by the shape of the curve (thus Cmin,ss and Cmax,ss).

Therefore, it is expected that the differences of approximately 20% in Cmax and Cmin at steady state between Qaialdo and Aldactone have no clinically relevant effect at steady state dosing. The issue with Cmax not falling within the bioequivalence margin is thus solved. Qaialdo can be considered as bioequivalent to the reference medicinal product Aldactone.

As Cmax of tested product was lower than Cmax of reference product, it is agreed that no safety issues are expected between products.

Besides the 5 ml syringe, the applicant will also be manufacturing a 1 ml syringe. Accuracy of administration with both syringes has been tested and confirmed, including the paediatric dosing.

Although the study did not show variability needed for replicate design, this issue is not pursued further as use of non-replicate design would not change the conclusions of the study.

2.4.3.1. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.4. Discussion on clinical aspects

There is a difference between bioavailability of Qaialdo and Aldactone due to the Cmax parameter not falling within the 80-125% confidence interval. Thus, the applicant was expected to provide a proof that the absence of comparable bioavailability between Qaialdo and Aldactone in Cmax will not have an impact on the pharmacodynamic response.

The applicant states that with regard to the correlation of pharmacokinetics and pharmacodynamic response, average concentration at steady state (Cave,ss) is more important and shows that Cave,ss is similar between Aldactone and Qaialdo. These parameters are however only estimated by the applicant from AUC0-tau after a single dose. This approach might be imprecise and may not correspond to the reality but the applicant also arguments with the fact that since spironolactone has a slow onset of action, a mere difference in Cmax is unlikely to affect the pharmacodynamic response.

The applicant was further asked to justify that the absence of comparability between Qaialdo and Aldactone in concentration-time (C-t) profile of spironolactone would not negatively affect the pharmacodynamic response to spironolactone**.**

The applicant stated that $C_{ave,ss}$ was considered more important for the pharmacological effect than $C_{max,ss}$ or $C_{min,ss}$. However, C-t profiles of spironolactone and its active metabolites for the oral tablet and suspension formulation under steady-state condition, using the single dose data and the superposition principle assuming linear pharmacokinetics, were not provided. This would have been required for at least once-daily and twice-daily dosing, since spironolactone can be taken either as a single daily dose or in divided doses.

To further substantiate the statement that $C_{ave,ss}$ is considered the most important for the pharmacological effect, exposure-response relationships or impact of the posology allowing the daily dosage to be given at various divided doses on exposure-response relationships was asked to be discussed as well.

To address the concentration-time profiles at steady-state for spironolactone, the applicant has conducted a post-hoc population pharmacokinetics (popPK) modelling and analysis. The assumption of linear pharmacokinetics is acceptable, and the population PK model appears fit-for-purpose as well given that simple superposition principle would also have been sufficient. The VPC plots, stratified by formulation, indicate that the popPK model is able to explain the central tendency well and overall variability of the observed PK data adequately.

The simulations show that total daily exposure for both regimens at steady state remains the same between both products, as is to be expected. Furthermore, the simulations show that mean Cmax for Qaialdo is 24% lower as compared to Aldactone after once daily dosing, and 22% lower after BID dosing.

Although Cmin,ss was not calculated and had to be derived from the C-t plots, it seems to be similar for once daily and twice daily dosing for both products.

Since the approved posology states that the dose can be divided for administration every 12h or 24h, it is clear that the efficacy is mainly driven by the total exposure (i.e. Cave,ss) and not by the shape of the curve (thus Cmin,ss and Cmax,ss).

Therefore, it may be expected that the differences of approximately 20% in Cmax and Cmin at steady state between Qaialdo and Aldactone have no clinically relevant effect at steady state dosing. The issue with Cmax not falling within the bioequivalence margin is thus solved. Qaialdo can therefore be considered as bioequivalent to the reference medicinal product Aldactone.

To be in line with the current praxis on wording of the paediatric indication the applicant was requested to specify and justify the lower age limit in the indication. Although limited data exist for the use of spironolactone in paediatric population a lower age limit is not set in the reference product Aldactone and therefore Aldactone has no restrictions on use with regard to age. As such no further data are needed to support the specification of paediatric population to neonates within the indication of Qaialdo. The oral suspension is particularly adapted for young children treatment. Consequently, the doses in children are clearly detailed in section 4.2 with dosage data for spironolactone from the WHO (WHO Model Formulary for Children, 2010) and Kindreformularium.

2.4.5. Conclusions on clinical aspects

Based on the presented bioequivalence study and PopPK analysis, Qaialdo is considered bioequivalent with Aldactone.

2.5. Risk Management Plan

2.5.1. Safety concerns

None.

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.>

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet 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.

3. Benefit-risk balance

This application concerns a hybrid version of spironolactone (oral suspension). The reference product Aldactone 100 mg film-coated tablets is indicated for:

In the management of refractory oedema associated with congestive cardiac failure; hepatic cirrhosis with ascites and oedema, malignant ascites, nephrotic syndrome, diagnosis and treatment of primary aldosteronism, essential hypertension.

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

No non-clinical studies have been provided for this application.

From a clinical perspective, this application contains 1 bioequivalence study.

The extension of CI range for Cmax to 70.00% - 143.00% cannot be justified based on the results from the bioequivalence study, as the model CV between periods was for Cmax 24.65 % and 19.92 %.

The test formulation of Qaialdo did not meet the protocol-defined criteria for bioequivalence when compared with the reference product. Specifically, the 90% confidence interval for the primary PK parameter Cmax was not contained within the protocol-defined acceptance range of 70.00% to 143.00%. Bioequivalence of the two formulations was thus not demonstrated.

The surrogate parameter, average concentration at steady state, although similar between test and reference, was only estimated by the applicant from AUC0-tau after a single dose. This approach might be imprecise and may not correspond to the reality.

The applicant was thus expected to provide additional information on concentration-time profiles.

The applicant has conducted a PopPK analysis, showing comparable concentration-time profiles at steady-state between Qaialdo and Aldactone for once and twice daily dosing. It can be thus assumed that the differences in Cmax will not have an impact on efficacy.

Having considered the data submitted in the application and available on the chosen reference medicinal product, no additional risk minimisation activities are required beyond those included in the product information.

Based on the review of the submitted data, comparability of Qaialdo to reference product Aldactone has been concluded. A positive benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Qaialdo is favourable in the following indication:

In the management of refractory oedema associated with congestive cardiac failure; hepatic cirrhosis with ascites and oedema, malignant ascites, nephrotic syndrome, diagnosis and treatment of primary aldosteronism, essential hypertension.

Neonates, children and adolescents should only be treated under guidance of a paediatric specialist. There is limited paediatric data available (see sections 5.1 and 5.2).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.