Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

# Public Assessment Report

# UK PAR

# Sodium Cromoglicate 100mg hard Capsules

# (sodium cromoglicate)

# UK Licence No: PL 44710/0008

# Kinedexe UK Limited

# LAY SUMMARY

## Sodium Cromoglicate 100mg hard Capsules (sodium cromoglicate)

This is a summary of the Public Assessment Report (PAR) for Sodium Cromoglicate 100mg hard Capsules (PL 44710/0008, formerly PL 41830/0023). It explains how the application for Sodium Cromoglicate 100mg hard Capsules was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Sodium Cromoglicate 100mg hard Capsules. For practical information about using Sodium Cromoglicate 100mg hard Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as 'Sodium Cromoglicate Capsules' in this report.

### What are Sodium Cromoglicate Capsules and what are they used for?

Sodium Cromoglicate Capsules are a 'generic medicine'. This means that Sodium Cromoglicate Capsules are similar to a 'reference medicine' already authorised in the UK called Nalcrom 100mg Capsules (PL 04425/0370; Aventis Pharma Limited (trading as Sanofi-Aventis or Sanofi), UK), which was first authorised in the UK on 14 September 1977.

Sodium Cromoglicate Capsules are used to treat allergic reactions to certain foods. This medicine is only used if the patient has had a test proving that he/she is allergic to these foods. As part of the patient's treatment, the doctor should advise the patient to avoid eating certain foods which may cause an allergic reaction.

### How do Sodium Cromoglicate Capsules work?

Sodium Cromoglicate Capsules contain the active substance, sodium cromoglicate, which belongs to a group of medicines called anti-allergics. Sodium cromoglicate works by stopping the release of the natural substances in the body that can cause an allergic reaction. It also lowers the body's response when the patient is exposed to substances to which he/she is allergic.

### How are Sodium Cromoglicate Capsules used?

Sodium Cromoglicate Capsules are for oral use (taken by mouth).

The patient should always take this medicine exactly as the doctor or pharmacist has advised. If unsure, the patient should ask the doctor or pharmacist.

**How much to take**
**Adults (including the elderly)**
• Two capsules, four times a day, before meals.
• When symptoms improve, the doctor may lower the patient's dose.

**Children (aged between 2 and 14 years)**
• One capsule, four times a day, before meals.
• When the child's symptoms improve, the child's doctor may lower the dose.

If signs of allergy do not improve within 2-3 weeks, the patient's doctor may double how much is taken. The patient's dose should not exceed 40 mg per kilogram of body weight per day.

If the patient feels that the effect of the treatment is too weak or too strong, he/she should NOT change the dose, but should ask his/her doctor.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

This medicine can only be obtained with a prescription.

**What benefits of Sodium Cromoglicate Capsules have been shown in studies?**

As Sodium Cromoglicate Capsules are a generic medicine, studies in patients have been limited to tests to determine that Sodium Cromoglicate Capsules are bioequivalent to the reference medicine Nalcrom 100mg Capsules (Sanofi-Aventis, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Sodium Cromoglicate Capsules?**

Like all medicines, Sodium Cromoglicate Capsules can cause side effects although not everybody gets them.

For the full list of all side effects reported with Sodium Cromoglicate Capsules, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Sodium Cromoglicate Capsules.

**Why are Sodium Cromoglicate Capsules approved?**

It was concluded that, in accordance with EU requirements, Sodium Cromoglicate Capsules have been shown to have comparable quality and to be bioequivalent to Nalcrom 100mg Capsules (Sanofi-Aventis, UK). Therefore, the MHRA decided that, as for Nalcrom 100mg Capsules (Sanofi-Aventis, UK), the benefits outweigh the identified risks and recommended that Sodium Cromoglicate Capsules can be approved for use.

**What measures are being taken to ensure the safe and effective use of Sodium Cromoglicate Capsules?**

A Risk Management Plan has been developed to ensure that Sodium Cromoglicate Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Sodium Cromoglicate Capsules, 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/reviewed continuously.

**Other information about Sodium Cromoglicate Capsules**

A Marketing Authorisation (PL 41830/0023) was granted in the UK to NRIM Limited on 01 March 2016. Following a change of ownership application, the Marketing Authorisation (PL 44710/0008) was granted to Kinedexe UK Limited on 01 April 2016.

The full PAR for Sodium Cromoglicate Capsules follows this summary.

For more information about treatment with Sodium Cromoglicate Capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2018.

# SCIENTIFIC DISCUSSION

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# Scientific discussion

## I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted NRIM Limited a Marketing Authorisation for the medicinal product Sodium Cromoglicate 100mg hard Capsules (PL 41830/0023) on 01 March 2016. The product may be referred to as 'Sodium Cromoglicate Capsules' in this report.

Sodium Cromoglicate Capsules are a Prescription Only Medicine (POM), which are indicated in adults and children (2 years and over) in patients with food allergy (where adequate investigations have been performed to determine sensitivity to one or more ingested allergens) in conjunction with restriction of main causative allergens.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application cross-referring to the reference product Nalcrom 100mg Capsules (PL 04425/0370; Aventis Pharma Limited (trading as Sanofi-Aventis or Sanofi), UK), which was first granted in the UK to Fisons Limited (PL 00113/0073) on 14 September 1977.

The active substance, sodium cromoglicate, is an antiallergic agent. It inhibits the release from mast cells of mediators of the allergic reaction. In gastrointestinal allergy the release of mediators can result in gastrointestinal symptoms or may allow absorption of antigenic material leading to systemic allergic reactions. Sodium cromoglicate is poorly absorbed from the gastrointestinal tract. Only about 1% is absorbed after an oral dose.

Three bioequivalence studies (two pivotal and one pilot) were submitted to support this application, comparing the applicant's test product Sodium Cromoglicate 100mg Capsules with the reference product Nalcrom (Sodium Cromoglicate) 100mg Capsules (Sanofi-Aventis, UK) under fasting conditions. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that the application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of Sodium Cromoglicate Capsules outweigh the risks and a Marketing Authorisation was granted. Following a Change of Ownership Application (COA) procedure, the Marketing Authorisation for Sodium Cromoglicate Capsules (PL 44710/0008) was granted to Kinedexe UK Limited on 01 April 2016.

## II QUALITY ASPECTS

### II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The medicinal product is available as transparent hard capsules, each with a circular double band on the body and the cap, containing white to off-white powder. Each capsule contains 100mg of sodium cromoglicate. The product also contains pharmaceutical excipients in the capsule shell, namely gelatin and printing ink (which contains shellac, propylene glycol, black iron oxide (E172) and potassium hydroxide). Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in white opaque high-density polyethylene containers each with a child resistant closure, in a pack size of 100 hard capsules.

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

## II.2 DRUG SUBSTANCE

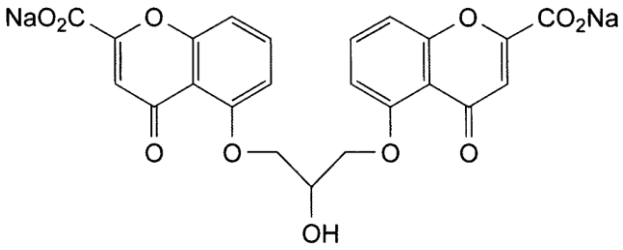
**Sodium cromoglicate**

INN: Sodium cromoglicate

Chemical Name: Disodium 5,5′-[(2-hydroxypropane-1,3-diyl)dioxy]bis(4-oxo-4H-1-benzopyran-2-carboxylate)

Molecular Formula: $C_{23}H_{14}Na_2O_{11}$

Structure




Molecular mass: 512.3

Appearance: White or almost white, hygroscopic, crystalline powder

Solubility soluble in water but practically insoluble in ethanol (96%)

Sodium cromoglicate is the subject of a European Pharmacopoeia monograph.

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

## II.3 MEDICINAL PRODUCT

**Pharmaceutical Development**

The objective of the development programme was to formulate a safe, efficacious, stable, hard capsule bioequivalent to the reference medicinal product, Nalcrom 100mg Capsules (Sanofi-Aventis, UK). Suitable pharmaceutical development data have been provided for this application.

Comparative *in-vitro* dissolution and impurity profiles have been provided for this product and the reference product. The dissolution profiles were satisfactory.

With the exception of printing ink, all the excipients comply with their respective European Pharmacopoeia monographs. Printing ink is controlled to a suitable in-house specification.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the EDQM to show that it is manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process.

The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on the first three full-scale production batches.

**Control of Finished Product**
The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months for the unopened product and 1 month for the product after first opening the container/bottle, with the special storage conditions 'Keep the bottle tightly closed in order to protect from moisture.' has been accepted. There are no special temperature storage conditions for this product.

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

**Bioequivalence/Bioavailability**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies.

### II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for Sodium Cromoglicate Capsules.

## III NON-CLINICAL ASPECTS

### III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of sodium cromoglicate are well known. As sodium cromoglicate is a well-known active substance, the applicant has not provided new non-clinical data for this application and none are required. An overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

### III.2 Pharmacology
The pharmacology of sodium cromoglicate is well known and adequately described in the applicant's non-clinical overview.

### III.3 Pharmacokinetics
The pharmacokinetic properties of sodium cromoglicate are well known and adequately described in the applicant's non-clinical overview.

### III.4 Toxicology
The pharmacokinetic properties of sodium cromoglicate are well known and adequately described in the applicant's non-clinical overview.

### III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, the risks to the environment are not expected to increase. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

### III.6 Discussion of the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

It is recommended that a Marketing Authorisation is granted for Sodium Cromoglicate Capsules, from a non-clinical point of view.

## IV. CLINICAL ASPECTS

### IV.1 Introduction.

The clinical pharmacology of sodium cromoglicate is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamic or pharmacokinetic data are provided or are required for this application.

In accordance with the regulatory requirements CPMP/EWP/QWP/1401/98 Rev 1/Corr**, Guideline on the Investigation of Bioequivalence, the applicant submitted three bioequivalence studies to support the applications comparing the applicant's test product Sodium Cromoglicate 100 mg Capsules with the reference product Nalcrom (Sodium Cromoglicate) 100 mg Capsules (Sanofi-Aventis, UK) under fasting conditions.

### IV.2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence studies:

Prior to the Pivotal Study 1 below, the applicant conducted an open label, balanced, randomized, two-treatment, two-sequence, two-period, crossover, single dose bioequivalence pilot study comparing the pharmacokinetics of the test product Sodium Cromoglicate 100mg Capsules with Nalcrom (Sodium Cromoglicate) 100mg capsules (Sanofi-Aventis, UK) in healthy, adult, human subjects under fasting conditions. The summary of pharmacokinetic parameters is as below:

| Pharmacokinetic Parameters (Units) | Test Geometric Mean | Reference Geometric Mean | T/R Ratio (%) | 90% CI Lower | 90% CI Upper | ISCV (%) |
|---|---|---|---|---|---|---|
| $C_{max}$ (ng / mL) | 6.95 | 5.73 | 121.32 | 81.35 | 180.95 | 58.22 |
| $AUC_{0-t}$ (ng*hr / mL) | 54.06 | 46.13 | 117.19 | 90.34 | 152.04 | 36.30 |
| $AUC_{0-inf}$ (ng*hr / mL) | 63.13 | 52.81 | 119.53 | 93.81 | 152.29 | 33.63 |

$AUC_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-inf}$ area under the plasma concentration-time curve from time zero to infinity
$C_{max}$ maximum plasma concentration
ISCV intra-subject coefficient of variability
Ratios and 90% CI calculated from log-transformed data

Based on the pilot biostudy results, the drug was considered to be a highly variable product, that is, the intra-subject variability was greater than 30 %. No statistical outliers were identified.

Since the pilot study was a two way crossover study, a true within subject variability for reference product was not obtained. Therefore the proposed pivotal study was planned as a full replicate, four way crossover design.

**Pivotal Study 1**

**An open label, randomised, two-treatment, four-period, two-sequence, single dose, four-way, full replicated, crossover study comparing the pharmacokinetics of the applicant's test product Sodium Cromoglicate 100 mg Capsules versus the reference product Nalcrom (Sodium Cromoglicate) 100 mg Capsules (Sanofi-Aventis, UK) in healthy, adult, male, human subjects under fasting conditions.**

The subjects were administered one capsule (100mg) of either the test or the reference product with 240 ml of water, after at least a 10-hour overnight fast. Blood samples were collected before and up to and including 48 hours after each administration. The washout period between the treatment phases was 14 days. Plasma concentrations of cromoglicic acid were analysed. The pharmacokinetic results are presented below:

**Table 1 Summary of the Main Pharmacokinetic Parameters of Sodium Cromoglicate 100mg Capsules**

| SUMMARY RESULTS | $C_{max}$ (ng/mL) | $AUC_{0-t}$ (ng*hr/mL) | $AUC_{0-inf}$ (ng*hr/mL) |
|---|---|---|---|
| **Untransformed Data** | | | |
| **TEST (T)** | | | |
| Arithmetic Mean | 5.318 | 38.666 | 44.755 |
| SD | 3.0937 | 22.0616 | 24.7511 |
| CV (%) | 58.18 | 57.06 | 55.30 |
| N | 26 | 26 | 26 |
| **REFERENCE (R)** | | | |
| Arithmetic Mean | 6.108 | 40.429 | 45.770 |
| SD | 4.1221 | 23.6340 | 24.1238 |
| CV (%) | 67.49 | 58.46 | 52.71 |
| N | 26 | 26 | 26 |
| **Log Transformed Data** | | | |
| LSM (T) | 1.47 | 3.50 | 3.65 |
| LSM (R) | 1.62 | 3.57 | 3.70 |
| Geometric Mean (T) | 4.36 | 32.95 | 38.55 |
| Geometric Mean (R) | 5.07 | 35.36 | 40.55 |
| T/R Ratio (%) | 85.88 | 93.20 | 95.07 |
| 90% CI (Calculated) | 73.45 — 100.43 | 82.67 — 105.06 | 84.37 — 107.12 |
| 90% CI (Range) | 69.84 - 143.19 | 80.00 - 125.00 | 80.00 - 125.00 |
| Power (%) | 76.00 | 92.23 | 92.40 |
| **Intra-subject CV (%)** | | | |
| Test | 54.26 | 39.54 | 35.11 |
| Reference | 36.47 | 29.42 | 32.23 |
| LSM= Least Squared Means; CI= Confidence Intervals; CV= Coefficient of Variance | | | |

$AUC_{0-t}$ area under the plasma concentration-time curve from time zero to the time of the last measurable analyte concentration (t)

$AUC_{0-inf}$ area under the plasma concentration-time curve from time zero to the time of the last measurable analyte concentration (t)

$C_{max}$ maximum plasma concentration

CV% coefficient of variation

Ratios and 90% CI calculated from log-transformed data

## Conclusion of Study 1

The 90% confidence intervals of the test/reference ratio of geometric means for $AUC_{0-t}$ and $AUC_{0-inf}$ lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). However, the 90% confidence limits for $C_{max}$ lie outside acceptable limits, even allowing for the claimed $C_{max}$ variability.

The applicant has claimed that sodium cromoglicate has a high intra-subject coefficient of variability (CV). In this pivotal study, the coefficient of variability for $C_{max}$ for the reference product was greater than 30% (36.47 %). Thus, in accordance with the bioequivalence guideline, the acceptance limits for $C_{max}$ can be widened to 76.45% and 130.81%; however the confidence interval observed for $C_{max}$ also lies outside this widened range.

As the 90% confidence intervals for $C_{max}$ lie outside the acceptable limits, the study does not demonstrate bioequivalence between the applicant's test product and the reference product. In response to objections raised, the applicant submitted the bioequivalence study below to support the application.

## Pivotal Study 2

**An open-label, balanced, randomised, single-dose, two-treatment, four-period, two-sequence, crossover, fully replicated, oral bioequivalence study comparing the pharmacokinetics of the applicant's test product Sodium Cromoglicate 100mg Capsules versus the reference product Nalcrom (Sodium Cromoglicate) 100mg Capsules (Sanofi-Aventis, U.K) in healthy, adult, human subjects under fasting conditions.**

The subjects were administered a single dose (one capsule) of either the test or the reference product with 240 ml of water, after at least a 10-hour overnight fast over four periods. Blood samples were collected before and up to and including 48 hours after each administration. The washout period between the treatment phases was 10 days. Plasma concentrations of cromoglicic acid were analysed. The pharmacokinetic results are presented below:

## Results

The main pharmacokinetic findings are summarised in Tables 2 and 3 below:

**Table 2 Geometric mean of Test product (T1, T2), Reference Product (R1, R2) of Cromoglicate**

| Pharmacokinetic Parameter | Geometric Mean | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Reference Replicate-1(R1) | N | Reference Replicate-2 (R2) | N | Test Replicate-1(T1) | N | Test Replicate-2 (T2) |
| $C_{max}$ (ng/mL) | 53 | 6.9319 | 53 | 6.6571 | 53 | 6.0247 | 53 | 6.1550 |
| $AUC_{0-t}$ (ng.hr/mL) | 53 | 44.7687 | 53 | 40.9559 | 53 | 40.0411 | 53 | 39.1033 |
| $AUC_{0-\infty}$ (ng.hr/mL) | 53 | 51.5680 | 53 | 49.2564 | 53 | 49.5165 | 52 | 49.9014 |
| $t_{max}$ (hr) | 53 | 2.64 | 53 | 2.50 | 53 | 3.10 | 53 | 2.52 |
| $K_{el}$ (1/hr) | 53 | 0.096378 | 53 | 0.077421 | 53 | 0.075821 | 52 | 0.075256 |
| $t_{1/2}$ (hr) | 53 | 7.1920 | 53 | 8.9530 | 53 | 9.1419 | 52 | 9.2106 |
| AUC_%Extrap_obs | 53 | 8.58 | 53 | 10.65 | 53 | 11.99 | 52 | 11.29 |

$C_{max}$ maximum plasma concentration
$AUC_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
Ratios and 90% CI calculated from log-transformed data

**Table 3 Statistical Evaluation of Test product (T) versus Reference product (R)**

| Pharmacokinetic Parameter | T/R Ratio % | 90% CI Lower | 90% CI Upper |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 89.68 | 80.86 | 99.46 |
| $AUC_{0-t}$ (ng.hr/mL) | 92.39 | 84.94 | 100.49 |

$C_{max}$ maximum plasma concentration
$AUC_{0-t}$ area under the plasma concentration-time curve from time zero to t hours

**Conclusion**
The 90% confidence intervals for the log-transformed parameters, $C_{max}$ and $AUC_{0-t}$ lie within the acceptable limits of 80.00% to 125.00%, in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**). Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Nalcrom (Sodium Cromoglicate) 100 mg Capsules (Sanofi-Aventis, UK), under fasting conditions.

## IV.3 Pharmacodynamics
The clinical pharmacodynamic profile of sodium cromoglicate is well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.

## IV.4 Clinical Efficacy
The clinical efficacy of sodium cromoglicate is well-known. No new efficacy data are presented or are required for this type of application.

## IV.5 Clinical Safety
The safety profile of sodium cromoglicate is well-known. With the exception of the safety data generated during the bioequivalence studies, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence studies.

## IV.6 Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Sodium Cromoglicate Capsules.

A summary of safety concerns is listed in the table below:

| Summary of safety concerns | |
|---|---|
| Important identified risk | • Hypersensitivity to the active ingredient or excipients |
| Important potential risk | • Use in pregnancy |
| Missing information | • Use in lactation |

Routine pharmacovigilance and routine risk minimisation activities are acceptable to monitor the safety concerns described in the Risk Management Plan.

## IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted for Sodium Cromoglicate Capsules.

# V. USER CONSULTATION
A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was English.

The results 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.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

### QUALITY

The important quality characteristics of Sodium Cromoglicate Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of sodium cromoglicate are well-known, no additional data were required.

### EFFICACY

With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant's product and the reference Nalcrom (Sodium Cromoglicate) 100 mg Capsules (Sanofi-Aventis, UK), under fasting conditions.

### SAFETY

With the exception of the safety data from the bioequivalence studies, no new data were submitted and none are required for this type of application. As the safety profile of sodium cromoglicate is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence studies.

### PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

### BENEFIT/RISK ASSESSMENT

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

### RECOMMENDATION

The grant of a Marketing Authorisation is recommended.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:


57 mm
57 mm
90 mm
Sodium Cromoglicate 100mg Capsules
100 capsules
100 mg
Sodium Cromoglicate 100mg Capsules
100 capsules
Each Capsule contains 100mg of Sodium Cromoglicate
For oral administration.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Keep the bottle tightly closed in order to protect from moisture.
Use as directed by your physician.
Sodium Cromoglicate 100mg Capsules
100 capsules
100 mg
Sodium Cromoglicate 100mg Capsules
100 capsules
POM PL 44710/0008
PL Holder: Kinedexe UK Limited, Unit 15, Moorcroft, Harlington Road, Uxbridge, UB8 3HD, UK
5 060090 470287
Batch No.:
Mfg. Date:
Exp. Date:
Unvarnished space for 2D data matrix

# Sodium Cromoglicate 100mg hard Capsules

# (sodium cromoglicate)

# PL 44710/0008

## STEPS TAKEN AFTER AUTHORISATION-SUMMARY

| Date submitted | Application type | Scope | Outcome |
|---|---|---|---|
| 25/06/2018 | Type II Complex | To register the submission of new bioequivalence data required as a result of Article 31 referral of Directive 2001/83/EC, Procedure No.: EMEA/H/A-31/1450. | Approved (22/08/2018) |
| | | | |
| | | | |

# ANNEX 1

| | |
|---|---|
| **Our Reference:** | PL 44710/0008 - 0012 |
| **Product:** | Sodium Cromoglicate 100mg hard Capsules |
| **Marketing Authorisation Holder:** | Kinedexe UK Limited |
| **Active Ingredient(s):** | Sodium cromoglicate |
| | |
| **Type of Procedure:** | National |
| **Submission Type:** | Variation |
| **Submission Category:** | Type II |
| **Submission Complexity:** | Complex |
| **EU Procedure Number (if applicable):** | Not applicable |

**Reason:**
To register the submission of new bioequivalence data required as a result of an Article 31 referral of Directive 2001/83/EC, as amended, Procedure No.: EMEA/H/A-31/1450.

**Supporting Evidence**
Bioequivalence clinical study report.

A statement has been provided that the study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP). The study is reviewed in accordance with the requirements set out in the guideline on the investigation of bioequivalence (Doc. Ref. CPMP/EWP/QWP/1401/98 Rev.1/Corr**).

The study site used for the submitted bioequivalence study has been inspected by the MHRA and is considered compliant.

**Evaluation**

***A randomised, single dose, open label, four-period, cross-over fully replicate bioequivalence study between Sodium Cromoglicate 100 mg capsules (Kindexe UK Limited, UK) and the reference product, Nalcrom® (Sodium Cromoglicate) 100 mg capsules (Sanofi-Aventis) in healthy adult human subjects under fasting conditions.***

Subjects received treatment in a cross-over fashion under fasting conditions according to the randomisation schedule. In each of the 4 periods, after an overnight fast of at least 10 hours, a single oral dose of one capsule of test or the reference product was administered orally with 240 mL of water. Subjects were not allowed to drink water for 1 hour before dosing until 2 hours post-dose except that given during administration of the dose and adverse event (AE) management if required. No food was permitted till 4 hours after dosing.

The treatment days were separated by a washout period of 14 days between period 1 and 2; 18 days between period 2 and 3; and 13 days between period 3 and 4. The four-period, fully replicate study design planned for each subject to be administered the test product and the reference product twice during the study, following one of two sequences: Ref/Test Ref/Test and Test/Ref Test/Ref.

Blood sampling (4 ml) was collected pre-dose and up to 72.00 hours post-dose in each period.

**Summary data**

**Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range)**

| **Treatment** | **$AUC_{0-t}$** **ng/ml/h** | **$AUC_{0-\infty}$** **ng/ml/h** | **$C_{max}$** **pg/ml** | **$t_{max}$** **h** |
|---|---|---|---|---|
| **Test** | **58.98 ± 29.17** | **65.78 ± 30.27** | **8.96 ± 5.15** | **2.33 (0.50-16.00)** |
| **Reference** | **55.63 ± 27.85** | **63.87 ± 33.29** | **8.34 ± 4.88** | **2.17 (0.50-12.00)** |
| | | | | |
| ***Ratio (90% CI)** | **104.64 (97.88 – 111.87)** | | **106.08 (97.70 – 115.17)** | |

**$AUC_{0-t}$** Area under the plasma concentration curve from administration to last observed concentration at time t. $AUC_{0-72h}$ can be reported instead of $AUC_{0-t}$, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products.

**$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when $AUC_{0-72h}$ is reported instead of $AUC_{0-t}$

**$C_{max}$** Maximum plasma concentration

**$t_{max}$** Time until $C_{max}$ is reached

***ln-transformed values (TestGeoLSM/RefGeoLSM); ABE (average bioequiavelence)*

**Conclusion**

Based on the submitted bioequivalence study, the test product, Sodium cromoglicate 100 mg capsules is considered bioequivalent with the reference product, Nalcrom® (Sodium cromoglicate) 100 mg capsules (Sanofi, UK), in healthy adult male human subjects under fasting conditions.

The application is approvable.

**Decision - Approve.**