COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ibusta 10 mg and 20 mg, hard modified-release capsules
(barnidipine hydrochloride)

NL/H/5244/001-002/DC

Date: 7 March 2023

This module reflects the scientific discussion for the approval of Ibusta 10 mg and 20 mg, hard modified-release capsules. The procedure was finalised at 14 February 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMS	Reference member state
RMP	Risk Management Plan
SmPC	Summary of medicinal Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the reference member state has granted a marketing authorisation for Ibusta 10 mg and 20 mg, hard modified-release capsules, from Sigillata Limited.

The product is indicated for mild to moderate essential hypertension.

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

For this decentralised procedure, concerning a generic application, essential similarity is claimed with European Reference Products (in the CMSs Poland and Bulgaria):

- Cyress 10, 10 mg capsules met gereguleerde afgifte (NL/H/0197/001; RVG 20554) and
- Cyress 20, 20 mg capsules met gereguleerde afgifte (NL/H/0197/002; RVG 20555)

from the MAH BModesto B.V. in Lelystad, the Netherlands. These products have been authorised in the Netherlands since 14 June 1999. In 2000, the mutual recognition procedure (MRP) of these products (NL/H/0197/001-002/MR) was finalised and approved.

There were no concerned member states (CMS) involved in the finalisation of this procedure.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Ibusta 10 mg hard modified-release capsules are size No.3 hard gelatin capsules filled with yellow to pale yellow pellets. The capsule cap is yellow with black ”1000” imprinting and the body is yellow with black ”0010” imprinting. Each capsule contains as active substance 10 mg of barnidipine hydrochloride, equivalent to 9.3 mg barnidipine.

Ibusta 20 mg hard modified-release capsules are size No.1 hard gelatin capsules filled with yellow to pale yellow pellets. The capsule cap is yellow with black ”1000” imprinting and the body is yellow with black ”0020” imprinting. Each capsule contains as active substance 20 mg of barnidipine hydrochloride, equivalent to 18.6 mg barnidipine.

The capsules are packed in oriented polyamide (OPA)/Aluminium/PVC-Aluminium perforated blisters.

The excipients are:
Capsule content – sugar spheres (containing sugar syrup, corn starch and sucrose), carboxy methyl ethyl cellulose, polysorbate 80, ethyl cellulose and talc,
Capsule shell – titanium dioxide (E171), yellow iron oxide (E172) and gelatin,
Printing ink – shellac, propylene glycol, black iron oxide (E172) and potassium hydroxide.

The capsule content of the two strengths are fully dose-proportional.

II.2 Drug Substance

The active substance is barnidipine hydrochloride (HCl), an established active substance not described in any pharmacopoeia. Barnidipine HCl is a pale yellow to yellow powder, which is soluble in methanol and very slightly soluble in water. The active substance contains two stereochemical centres, it therefore exhibits optical isomerism. Barnidipine HCl is obtained as enantiomer (S,S configuration). In addition, the drug substance exhibits polymorphism. Within the manufacturing process, form I of barnidipine HCl is produced.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The synthesis route for barnidipine HCl consists of two chemical steps, comprising of one isolated intermediate followed by a chiral resolution by crystallisation and subsequently three purification steps and one final crystallisation step. No class 1 solvents or heavy metal catalysts are used during the manufacturing process. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification is established in-house by the MAH and contains requirements for: description, identification, water content, sulphated ash, (R,R) enantiomer, related substances, assay and residual solvents. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production batches of barnidipine HCl.

Stability of drug substance
Stability data on the active substance have been provided for three production scaled batches stored at 25°C/60% RH (36 months), 30°C/75% RH (36 months) and 40°C/75% RH

(6 months). No significant changes and no trends are observed in any of the parameters studied under all conditions. Based on the stability data provided, a re-test period of 48 months was granted.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The drug product development is strongly based on the qualitative composition and dissolution performance of the reference product Cyress 20, 20 mg modified release capsules. The differences between the proposed product and the reference product are: the use of sugar spheres (instead of sucrose) in the capsule core, and the use of a different colourant in the hard gelatin capsule shell. These differences have been adequately discussed and have been found acceptable. The dissolution methods are adequately described, as well as the optimisation trials used in the manufacturing process development.

The MAH provided supportive dissolution data for the requested strength biowaiver for the 10 mg. The data confirm that appropriate *in vitro* data are adequate to waive additional *in vivo* bioequivalence testing for the 10 mg strength (see section IV.2 for more info). The dissolution was investigated according to the EMA Bioequivalence guideline. Dissolution was low for all strengths (10 g and 20 mg) and at all pHs (pH 1.2, 4.5 and 6.8). The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar. Therefore, along with the other criteria discussed in section IV.2, the strength biowaiver for the 10 mg could be granted.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for several batches in accordance with the relevant European guidelines. This included (but was not limited to) three batches of 10 mg and two batches of 20 mg for dissolution validation.

Control of excipients

The specifications for all the content excipients comply with the Ph.Eur., except carboxy methyl ethyl cellulose (CMEC), for which adequate in-house specifications are set. The MAH provided descriptions of analytical procedures for CMEC, which were based on the monograph of CMEC in the Japanese Pharmaceutical Excipients 2018. Therefore, these specifications were acceptable and further validation data were not required. The specifications for the excipients in the hard capsules (No.1 and No.3) are considered usual and acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identity (high- performance liquid chromatography (HPLC) retention time (RT) and HPLC ultra-violet (UV)), assay,

impurities / degradation products, dissolution, uniformity of dosage units and micro-biological quality. One impurity was identified and no routine test was deemed necessary because the levels were below 10% of the limit. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The in-house HPLC methods have been adequately validated, the microbial test method was adequately verified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

A risk evaluation has been performed for the presence of nitrosamines in the active substance, the finished product, or the packaging, based on the EMA notice "Information on nitrosamines for marketing authorisation holders (EMA/189634/2019)". The MAH demonstrated there is no risk for nitrosamine formation.

Stability of drug product

Stability data on the product have been provided for three batches of each strength in accordance with applicable European guidelines, demonstrating the stability of the product for 24 months at 25°C/60% RH, packaged in aluminium/aluminium blisters, and for 6 months at accelerated conditions of 40°C/75% RH. Dissolution results show some variability, but results remain within the specification limits. Assay results remain consistent and do not show a significant trend. The storage conditions are in accordance with those of the originator product Cyress: Do not store above 25°C. This was considered appropriate for Ibusta. A photostability study showed that the product was not sensitive to light. On basis of the data submitted, a shelf life was granted of 2 years, with storage conditions: Do not store above 25°C.

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

Certificates of suitability issued by the EDQM have been provided for gelatin and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated. There are no other substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

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

III.2 Discussion on the non-clinical aspects

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

IV. CLINICAL ASPECTS

IV.1 Introduction

Barnidipine hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member state found that no further clinical studies were required besides the three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Ibusta 20 mg, hard modified-release capsules (Sigillata Limited, Ireland) is compared with the pharmacokinetic profile of the reference product Cyress 20, 20 mg modified-release capsules (BModesto B.V., The Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH was granted a biowaiver for *in vivo* bioequivalence studies for the 10 mg strength, based on these criteria:

a) both the 10 mg and 20 mg strengths are manufactured by the same manufacturing process,
b) the qualitative composition of both strengths are the same,
c) the composition of the capsule fill of both strengths are quantitatively proportional,
d) appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing. The dissolution was investigated according to the EMA Bioequivalence guideline.

The results of the studies with the 20 mg formulation can be extrapolated to the 10 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6).

Bioequivalence studies

The MAH submitted the reports of two single-dose bioequivalence studies (one fed, one fasted) using the highest strength (20 mg). The information in the SmPC states that Ibusta can be taken before, during and after a meal. This was followed by a third bioequivalence study; multiple-dose under fasted conditions.

Study 1 – single dose, 20 mg, under fasted conditions

Design

A open-label, randomised, single-dose, full replicate, cross-over, bioequivalence study was carried out under fasted conditions in 100 healthy male subjects, aged 19-43 years. Each subject received a single dose (20 mg) of one of the two barnidipine formulations. The capsule was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were four dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

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

Results

A total of 17 subjects did not complete the study. Eight subjects were excluded prior to dosing in Period II (two due to not reporting, five due to non-compliance, one due to an adverse event). Therefore 92 subjects were dosed in Period II. Eighty-nine subjects completed Period II of the study and two subjects were withdrawn due to adverse events. Eighty-six subjects entered Period III (three subjects did not report and three subjects were excluded due to non-compliance) and 84 subjects completed Period III (one was withdrawn due to adverse events and one withdrew consent). Eighty-three subjects entered and completed Period IV (two subjects did not report and one subject was excluded due to non-

compliance). This resulted in a total of 91 subjects being included in the pharmacokinetic analysis. The reasons for the withdrawal/discontinuation of the 17 subjects were acceptable.

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

Treatment N=91	AUC_{0-72} (h.pg/mL)	$AUC_{0-\infty}$ (h.pg/mL)	C_{max} (pg/mL)	t_{max} (h)
Test	9781 ± 7281	10406 ± 7597	1591 ± 1211	6 (4.5-9.0)
Reference	10371 ± 7789	11056 ± 8095	1716 ± 1380	6 (4.5-10)
***Ratio (90% CI)**	0.94 (0.86 - 1.03)	0.97 (0.89 – 1.06)	0.93 (0.83 – 1.04)	--

AUC_{0-72}	Area under the plasma concentration curve from administration to 72 hour.
$AUC_{0-\infty}$	Area under the plasma concentration curve from administration to infinity.
C_{max}	Maximum plasma concentration
t_{max}	Time until C_{max} is reached

**ln-transformed values*

Study 2 – single dose, 20 mg, under fed conditions

Design

A open-label, randomised, single dose, full replicate, cross-over bioequivalence study was carried out under fed conditions in 100 healthy male subjects, aged 18-43 years. Each subject received a single dose (20 mg) of one of the two barnidipine formulations. The capsule was orally administered with 240 mL water after an overnight fast of 10 hours, followed by a high-calorie, high-fat breakfast consumed within the 30 minutes before dosing. There were four dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 11, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

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

Results

A hundred subjects entered, 99 were dosed and 93 completed Period I. Eighty subjects were excluded prior to dosing in Period II (five due to not reporting, two for non-compliance, one withdrew consent). Eighty-nine subjects were dosed in Period II and 87 subjects completed Period II of the study, (two subjects were withdrawn because the breakfast was not consumed). Eighty-one subjects entered Period III (seven subjects did not report and four subjects were excluded due to non-compliance) and 81 subjects completed Period III.

Seventy-five subjects entered Period IV (nine subjects did not report) and all these subjects completed Period IV. A total of 90 subjects completed at least two periods of the study and were therefore eligible for pharmacokinetic analysis. The reasons for the withdrawal/ discontinuation of the 25 subjects are acceptable.

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

Treatment	AUC_{0-72} (h.pg/mL)	AUC_{0-inf} (h.pg/mL)	C_{max} (pg/mL)	t_{max} (h)
Test	19618 ± 7235	20447 ± 7529	3870 ± 1600	7.0 (4.0-11.05)
Reference	21468 ± 8108	22677 ± 8109	4461 ± 2038	6.5 (4.0-10.0)
***Ratio (90% CI)**	0.92 (0.87 – 0.97)	0.90 (0.87 – 0.93)	0.83 (0.77 – 0.90)	--

AUC_{0-72}	Area under the plasma concentration curve from administration to 72 hour.
AUC_{0-inf}	Area under the plasma concentration curve from administration to infinity.
C_{max}	Maximum plasma concentration
t_{max}	Time until C_{max} is reached

**ln-transformed values*

Study 3 – multiple dose, 20 mg, under fasted conditions

The barnidipine products in the bioequivalence studies are modified release capsules and accumulation following repeated dosing may occur. According to the EMA guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms, the accumulation in repeated dosing is negligible when AUC_{0-24}/AUC_{∞} is >90%. This value was <90% in the single-dose studies, therefore the possibility of accumulation was not excluded and bioequivalence could not be confirmed based on those studies alone. In response, the MAH performed a multiple-dose bioequivalence study, using the highest strength (20 mg) under fasted conditions.

Design

A open-label, randomised, two-period, two-sequence, multiple-dose (6 dosages per period), oral bioequivalence study was carried out under fasted conditions in 80 healthy male subjects, aged 18-71 years. Each subject received six doses (one dose of 20 mg in the morning of days 1 to 6) of one of the two barnidipine formulations. The capsule was orally administered with 240 mL water after an overnight fast of at least 10 hours, followed by 2.5 hours of fasting. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose (prior to the first, second, third, fourth and fifth dose) and at 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 112, 119.9 (prior to the sixth dose), 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 136, and 143.9 hours post administration of the products.

The design of the study is acceptable.

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

Results
Eighty subjects entered and were dosed and 78 subjects completed Period I. Seventy-four subjects completed the study (six subjects were drop-outs due to personal reasons and non-compliance). The reasons for the withdrawal/ discontinuation of the six subjects are acceptable. This resulted in a total of 65 subjects for whom steady-state status was confirmed, who were eligible for pharmacokinetic analysis (table 3). Pharmacokinetic and statistical analysis was also performed for the total of 74 subjects who completed the study, including the nine for whom steady-state was not shown (table 4).

Table 3. Pharmacokinetic parameters of the 65 subjects that reached steady-state (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of barnidipine, multiple-dose, under fasted conditions.

Treatment N=65	$(AUC_{0\text{-}tau})_{ss}$ (pg/mL*h)	$C_{max,ss}$ (pg/mL)	$C_{tau,ss}$ (pg/mL)	$t_{max,ss}$ (h)
Test	3190.0 ± 2416.8	463.6 ± 421.0	50.8 ± 33.7	6 (3-9)
Reference	2868.2 ± 2103.4	402.8 ± 340.2	46.8 ± 31.5	7 (3-9)
***Ratio (90% CI)**	1.15 (1.07-1.24)	1.19 (1.07-1.33)	1.10 (1.05-1.16)	-

$(AUC_{0\text{-}tau})_{ss}$	Area under the curve during the dosing interval
$C_{max,ss}$	Maximum drug concentration obtained directly from the data (without interpolation)
$C_{tau.ss}$	Plasma drug concentration at the end of the dosing interval, at steady-state
$t_{max.ss}$	Time of the peak drug concentration during the dosing interval

**ln-transformed values*

Table 4. 90% Confidence Interval of barnidipine of all 74 subjects (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment N=74	$(AUC_{0\text{-}tau})_{ss}$ (pg/mL/h)	$C_{max,ss}$ (pg/mL)	$C_{tau,ss}$ (pg/mL)
***Ratio (90% CI)**	1.13 (1.05-1.22)	1.09 (1.04-1.14)	1.15 (1.03-1.27)

$(AUC_{0\text{-}tau})_{ss}$	Area under the curve during the dosing interval
$C_{max,ss}$	Maximum drug concentration obtained directly from the data (without interpolation)
$C_{tau.ss}$	Plasma drug concentration at the end of the dosing interval, at steady-state

**ln-transformed values*

Conclusion on bioequivalence studies

In the single dose studies (Study 1 and 2) The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} and for are within the bioequivalence acceptance range of 0.80 – 1.25.

In the multiple dose study (Study 3), the intra-subject variability was 47.60% for the reference. Based on this, the acceptance range for $C_{max,ss}$ was allowed to be widened to 70.93-140.98% (according to the bioequivalence guidance). Bioequivalence is shown for $AUC_{0-tau,ss}$, $C_{max,ss}$ and $C_{tau,ss}$ between the test and reference product as their 90% confidence intervals (CI) are within the set limits for both the 65 subjects for which steady-state was confirmed and for all 74 subjects that finished the BE study (including the 9 subjects for which steady-state was not confirmed).

Based on the submitted bioequivalence studies, Ibusta 20 mg, hard modified-release capsules is considered bioequivalent with Cyress 20, 20 mg modified-release capsules. A biowaiver was granted for the 10 mg strength and Ibusta 10 mg, hard modified-release capsules is considered bioequivalent with Cyress 10, 10 mg modified-release capsules.

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

IV.3 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 Ibusta.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Cyress. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the products is similar to the pharmacokinetic profile of this reference products. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference products.

V. USER CONSULTATION

The package leaflet (PL) 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 PL was English. The test consisted of a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Ibusta 10 mg and 20 mg, hard modified-release capsules have a proven chemical-pharmaceutical quality and are generic forms of Cyress 10, 10 mg modified-release capsules and Cyress 20, 20 mg modified-release capsules. Cyress is a well-known medicinal product with an established favourable efficacy and safety profile.

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

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). The member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ibusta with the reference product, and has therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 February 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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