INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER

NAME OF PRODUCT: **Nabilone Placebo Capsules**

DRUG SUBSTANCE: **none**

Contents

2.1.P.1 Description and Composition of the Drug Product

Description

Nabilone placebo capsules are an oral dosage form in white/white hard gelatine capsules size 4. Each capsule contains 113 mg corn starch as filler. The final product is packaged into PE bottles. Each PE bottle contains 28 capsules.

Composition

The Nabilone placebo capsules consist of the following compounds:

- Corn starch

The quantitative composition per capsule is presented below.

Substance	Composition Nabilone placebo (g/manufacturing step *)	Composition Nabilone placebo (mg/Capsule **)	Function
Corn starch	11.3	113 (21 ml)	Filler

* 100 capsules per manufacturing step
** Net capsule weight is approx. 38 mg and capsules are of capsule size 4.

Hard gelatine capsules used for Nabilone placebo consist of a white cap and a white body, both opaque, with the composition and the amount of ingredients given in the figures below.

Composition of capsule cap (white opaque)

Name of excipient	Function	Amount [%]	mg/Cap
Titanium dioxide (E171)	Opacifier	2	0.3040
Gelatine q.s.	Structure	98	14.8960
Total		100	15.2000

Composition of capsule body (white opaque)

Name of excipient	Function	Amount [%]	mg/Body
Titanium dioxide (E171)	Opacifier	2	0.4560
Gelatine q.s.	Structure	98	22.3440
Total		100	22.8000

Container

White 50 ml Duma Twist-Off containers made of high density polyethylene (HDPE) and the tamper-evident Twist-Off caps made of polypropylene (PP) containing a desiccant are used.

Pack size: 28 capsules per container.

All components conform to the current requirements of food and medicinal products packaging.

2.1.P.2 Pharmaceutical Development

Capsule Content

The excipient used as a filler for placebo capsules is corn starch. It is well known as indifferent and therefore often used in above mentioned functionality in oral pharmaceutical products.

The amount of corn starch is responsible for a proper filling volume of the capsules compared to the capsules containing active substance.

No other excipients are used.

Capsule Shell

Gelatine is commonly used as forming material of pharmaceutical capsules. For Nabilone placebo Titanium dioxide (E171) is used as an opacifier.

Composition of capsule cap (white opaque)

Name of excipient	Function	Amount [%]	mg/Cap
Titanium dioxide (E171)	Opacifier	2	0.3040
Gelatine q.s.	Structure	98	14.8960
Total		100	15.2000

Composition of capsule body (white opaque)

Name of excipient	Function	Amount [%]	mg/Body
Titanium dioxide (E171)	Opacifier	2	0.4560
Gelatine q.s.	Structure	98	22.3440
Total		100	22.8000

2.1.P.3 Manufacture

2.1.P.3.1 Manufacturer

The manufacture and testing of Nabilone placebo capsules drug product is being performed at:

Site	Responsibilities
Allerheiligenapotheke Mag. Pharm. Herbert Baldia KG Allerheiligenplatz 4 1200 Wien Austria	• Manufacture of drug product • Testing of drug product • Packaging of drug product
Mikrobiologisches Prüflabor GmbH Grabenweg 68 6020 Innsbruck Austria	• Microbiology testing of drug product
Kwizda Pharmadistribution GmbH Achauer Straße 2 2333 Leopoldsdorf Austria	• Secondary packaging site

2.1.P.3.2 Batch Formula

The batch formula of Nabilone placebo is provided in the table below.

Table 1: Batch Formula (per 100 capsules of Nabilone placebo)

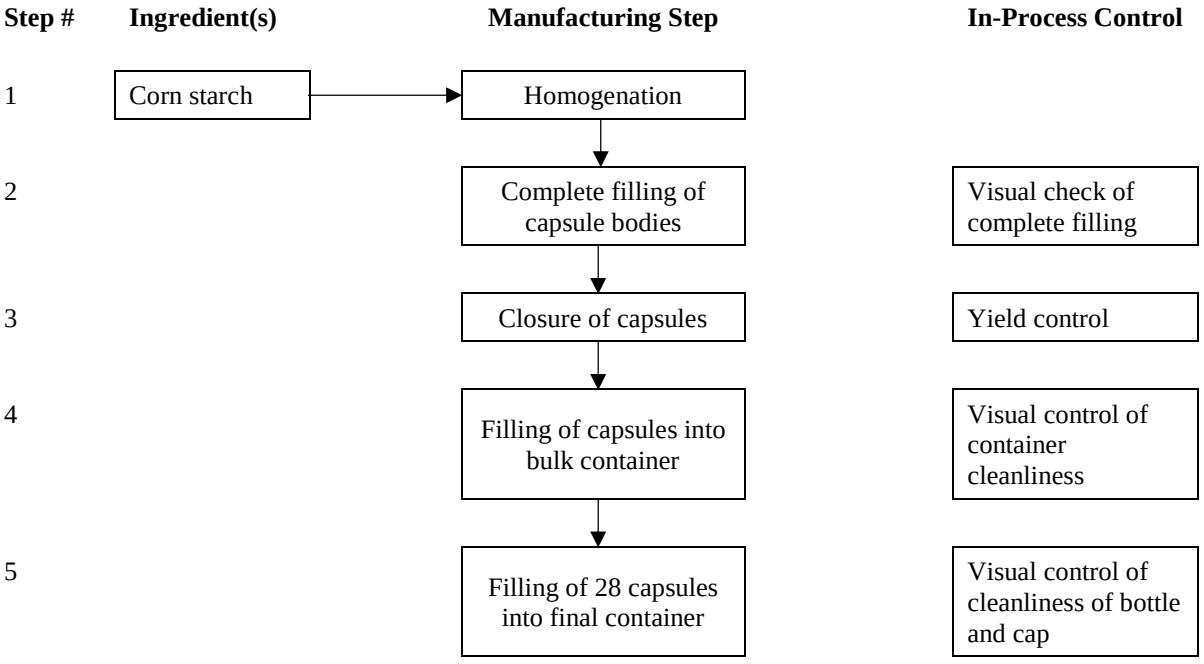
Ingredient	Amount		Function
	Per capsule [mg]	Per sub-batch [g] (100 pcs)	
Corn starch	113	11.3	Filler

2.1.P.3.3 Description of Manufacturing Process and Process Controls

The manufacturing of Nabilone placebo capsules can be divided into the following stages:

Stage	Manufacturing step
Stage 1	Homogenation of corn starch
Stage 2	Complete filling of capsule bodies with corn starch
Stage 3	Closure of capsules
Stage 4	Filling of capsules into bulk container
Stage 5	Filling of 28 capsules into final bottles

Flow chart



2.1.P.4 Control of Excipients

2.1.P.4.1 Specifications

The excipient used in the drug product formulation complies with the current valid edition of the Ph. Eur.

Table 1: Compendial Quality Standard of Excipient

Excipient	Quality Standard	Supplier*
Corn starch	Ph. Eur.	CAESAR & LORETZ GmbH Hilden, Germany
Placebo capsules Gelatine Titanium dioxide, E171	 Ph. Eur. Ph. Eur.	Capsugel Bornem, Belgium

*Current supplier. The applicant reserves the right to source inactive ingredients from other manufacturers; the grade of material will be equivalent and the supplier(s) suitably qualified.

CoA Corn Starch

QUALITÄTSKONTROLLE
CAESAR & LORETZ GmbH
Herderstr. 31
40721 Hilden
Tel.: 02103/49940

Analysenzertifikat

0005

Produkt	**10a**	**Maisstärke**
Synonym		**Maydis amylum**
Engl. Bezeichnung		**Maize starch**
Charge	**153109**	
Prüfvorschrift	**PH.EUR. 8.0**	
Verfalldatum	**06.2020**	

Prüfung	Spezifikation	Ergebnis
Eigenschaften	Gemäss Prüfvorschrift	Entspricht
-Aussehen	Gemäss Prüfvorschrift	Entspricht
-Löslichkeit	Gemäss Prüfvorschrift	Entspricht
Identität	Gemäss Prüfvorschrift	Entspricht
-Prüfung A	Gemäss Prüfvorschrift	Entspricht
-Prüfung B	Gemäss Prüfvorschrift	Entspricht
-Prüfung C	Gemäss Prüfvorschrift	Entspricht
Reinheit	Gemäss Prüfvorschrift	Entspricht
-pH-Wert	4,0 - 7,0	4,6
-Fremde Bestandteile	Nicht vorhanden	Negativ
-Oxidierende Substanzen	Max 20 ppm	Max 20 ppm
-Schwefeldioxid	Max 50 ppm	Max 50 ppm
-Eisen	Max 10 ppm	Max 10 ppm
-Trocknungsverlust	Max 15,0 %	11,3 %
-Sulfatasche	Max 0,6 %	0,1 %
Mikrobielle Verunreinigung	Gemäss Prüfvorschrift	Entspricht
-TAMC (KBE/g)	Max 1000	15
-TYMC (KBE/g)	Max 100	Max 10
-Escherichia coli	Nicht vorhanden	Negativ
-Salmonellen	Nicht vorhanden	Negativ
Ergebn.entspr.Prüfvorschr.	*****	Ja

CoA Capsules (Nabilone placebo)

TO THE ATTENTION OF:

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CERTIFICATE OF ANALYSIS

Page: 1 of 2

The capsules are produced under very carefully controlled conditions. Controls are performed continuously throughout the process and guarantee that capsules conform to the highest quality standards. The capsules described below conform to the specifications as defined in the current edition of the Capsugel "Technical Reference File" for empty hard gelatin capsules.

PRODUCT DESCRIPTION Empty Hard Gelatin Capsules (Bovine and/or Porcine Origin)

Customer:		Lot Number:	34435641
Product Name:		Customer Reference:	
Product Code:		Product Size:	4
Manufacturing Date:	26-Apr-2016	Type:	CONI-SNAP
Expiration Date:	Apr 2021		
BODY		**CAP**	
Code:	44.000	Code:	44.000
Name:	WHITE OP.	Name:	WHITE OP.

Body Composition		**Cap Composition**	
Titanium dioxide	2.0000 %	Titanium dioxide	2.0000 %
GELATIN	qsp 100 %	GELATIN	qsp 100 %

Due to the nature of raw materials, their sourcing, and technology improvements, the color composition data indicated are target values and actual values may vary to insure the consistency of lot color. Capsugel supports the expiry date if recommendations for warehousing and transportation are observed (recommended : 15°C - 25°C and 35% - 65% relative humidity)

Ingredient / Reference	**E Nr**	**C.I. Nr**	**Function**	**Regulatory References**
Titanium dioxide	E171	77891	Opacifier	(EU) 231/2012, 21 CFR, EP, JP, USP/NF
GELATIN			Structure	EP, JP, USP/NF

ANALYTICAL DATA

Characteristics	**Test Method**	**Units**	**Specifications**	**Results**
Identification of gelatin	CP010		Positive	pass *
Identification of TiO2	CP011		Conforms to composition	pass *
Sulphated ash	CP015	%	Less than 7	pass *
Arsenic	CP017A	ppm	Less than 1	pass *
Cadmium	CP017B	ppm	Less than 0.5	pass *
Lead	CP017C	ppm	Less than 1	pass *
Mercury	CP017D	ppm	Less than 0.1	pass *
Lubricant content	CP019	%	Less than 0.5	0.04 *
Sulphur dioxide	CP020	ppm	Less than 50	2 *
Disintegration time	CP001	min/sec	Less than 15:00	2:48 *
Loss on drying	CP014	%	13.0 to 16.0	14.5
Average weight	CP003	mg	35 to 41	38.4
Total Aerobic Microbial Count	CP031	cfu / g	Less than 1000	< 10
Escherichia coli	CP033		Absence in 1 gram	pass *
Salmonella	CP034		Absence in 10 gram	pass *
Staphylococcus aureus	CP035		Absence in 1 gram	pass *
Pseudomonas aeruginosa	CP036		Absence in 1 gram	pass *
Total Yeasts/Moulds Count	CP032	cfu / g	Less than 100	< 10 *

*** Reduced frequency testing**

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CERTIFICATE OF ANALYSIS

Customer Name: Lot Nr: 34435641

Capsugel hard gelatin capsules are meeting not more than 2 ppm Chromium as defined in the Chinese pharmacopoeia for Vacant Gelatin Capsules.
In accordance with ICH Q3C residual solvent guideline , Class 3 Solvents may be used according to good manufacturing practices such that their cumulative value does not exceed 5000ppm or 0.5%, under option 1 as defined in ICH Q3C, USP<467>, and EP General Text 5.4.

Physical Characteristics

This product conforms to established A.Q.L.'s for Physical Attributes.
Appearance - Clean empty capsules, meeting the specified requirements of color and size.
Odor - Free of disagreeable odor.
The reported disintegration time is subjective, and is provided to indicate Pass/Fail status for 15 minutes.
Tests for odor, solubility and acidity conform to Japanese Pharmacopeia requirements.

TSE/BSE Regulations

Capsugel can use blends of several pharmaceutical gelatins. When bovine gelatin is used by Capsugel, it is in full compliance with all pharmaceutical regulatory statutes.
Specifically, Capsugel fully complies with the following where applicable:

- Commission Directive 2003/63/EC/ Note for guidance EMA/410/01 compliance demonstrated by "Certificate of Suitability".
- Regulation (EC) No 853/2004 on specific hygiene rules for food of animal origin.
- Regulation (EC) No 999/2001 as regards specified risk material.
- United States FDA - 21 CFR Parts 211, 226, 300, 500, 530, 600, 895, and 1271 related to Use of Materials Derived from Cattle in Medical Products.
- United States FDA - 21 CFR Parts 189 and 700 related to Use of Materials Derived From Cattle in Human Food and Cosmetics.
- Japanese Ministry of Health, Labor Welfare (MHLW) - "Food Sanitation Law", MHLW Notice No.0327-2 of March 27, 2015.
- Japanese Ministry of Health, Labor and Welfare - Notification No. 210, Notification No. 1002-27 as of November 25th 2014.
- The raw material is derived from healthy animals slaughtered in a slaughterhouse, which have been inspected by an official veterinarian and have been deemed fit for human consumption.

Capsugel currently manufactures capsules under any (or all) of the following Certificates of Suitability:

- Rousselot R1 CEP 2000-027
- Rousselot R1 CEP 2000-029
- Rousselot R1 CEP 2001-332
- PB Gelatins R1 CEP 2000-045
- PB Gelatins R1 CEP 2002-110
- Gelita group R1 CEP 2001-424
- Gelita group R1 CEP 2003-172
- Sterling Gelatin R1-CEP 2001-211
- Nitta Gelatin R1-CEP 2000-344
- Nitta Gelatin R1 CEP 2005-217
- Nitta Gelatin R1 CEP 2004-247
- Nitta Gelatin R1 CEP 2004-320

Manufacturing Processes:
No Addition of Preservatives
No Ethylene Oxide Treatment
No Irradiation Treatment

Capsugel Belgium NV
Sophie De Keersmaeker - Quality Assurance
Rijksweg 11 - 2880 Bornem -Belgium
Tel: +32 (0)3 8900588

Digitally approved by Soontjens, Chris (May 03 2016, 12:24:46)
Authorized Signer

2.1.P.4.2 Analytical Procedures

For the excipients described in the Ph. Eur., the analytical procedures are identical with those mentioned in the respective monographs.

2.1.P.4.3 Validation of Analytical Procedures

All analytical procedures are performed according to the current Ph. Eur.

2.1.P.4.4 Justification of Specifications

The excipient specifications are equivalent to those of their respective Ph. Eur. monograph.

2.1.P.4.5 Excipients of Human or Animal Origin

The only material of human or animal origin is the gelatine used for manufacture of the capsule shell material. The gelatine used by the current manufacturer Capsugel can contain blends of several pharmaceutical gelatines. When bovine gelatine is used, it is in full compliance with all pharmaceutical regulatory requirements.

Regulatory declaration by Capsugel regarding BSE safety is attached on the following pages.

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Regulatory Information & Documents

> **Subject** – Regulatory declaration – BSE safety

Valid as of September 2015

Capsugel can use blends of several pharmaceutical gelatins. When bovine gelatin is used by Capsugel, it is pharmaceutical grade, and in full compliance with all pharmaceutical regulatory statutes. Specifically, Capsugel fully complies with the following where applicable:

- Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3), which is published by the European Commission following Commission Directive 2003/63/EC, (amending Directive 2001/83/EC on the Community code relating to medicinal products for human use), Annex I, Part I, paragraph 3.2.2.4. Control of excipients.
  These Directives require that applicants for Marketing Authorisation must demonstrate that medicinal products are manufactured in accordance with the latest version of this Note for Guidance and compliance is demonstrated by the "Certificate of Suitability" issued to the manufacturer of the bovine gelatin by the European Directorate for the Quality of Medicines (EDQM). As such, Capsugel currently manufactures capsules under any (or all) of the following Certificates of Suitability:

  - Rousselot R1-CEP 2000-027
  - Rousselot R1-CEP 2000-029
  - Rousselot R1-CEP 2001-332
  - PB Gelatins R1-CEP 2000-045
  - PB Gelatins R1-CEP 2002-110
  - Gelita Group R1-CEP 2001-424
  - Gelita Group R1-CEP 2003-172
  - Sterling Gelatin R1-CEP 2001-211
  - Nitta Gelatin R1-CEP 2000-344
  - Nitta Gelatin R1-CEP 2004-247
  - Nitta Gelatin R1-CEP 2004-320
  - Nitta Gelatin R1-CEP 2005-217

- Regulation (EC) No 853/2004 laying down specific hygiene rules for food of animal origin.
- Regulation (EC) No 999/2001 laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies.

- United States Food and Drug Administration (FDA) – Proposed Rule on "Use of Materials Derived from Cattle in Medical Products Intended for Use in Humans and Drugs Intended for Use in Ruminants," 72 Fed. Reg. 1582 (Jan. 12, 2007) (to be codified at 21 CFR Parts 211, 226, 300, 500, 530, 600, 895, and 1271).
- United States Food and Drug Administration (FDA) – Interim Final Rule on "Use of Materials Derived From Cattle in Human Food and Cosmetics," 69 Fed. Reg. 42256 (July 14, 2004), as amended and codified at 21 CFR §§ 189.5, 700.27; and Final Rule on "Recordkeeping Requirements for Human Food and Cosmetics Manufactured From, Processed With, or Otherwise Containing, Material From Cattle," 71 Fed. Reg. 59653 (Oct. 11, 2006), codified at 21 CFR §§ 189.5, 700.27.

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CAPSUGEL®

Regulatory Information & Documents

- Japanese Ministry of Health, Labor Welfare (MHLW) - "Food Sanitation Law", Chapter 2, Article 7 and Article 10 "Specifications and Standards for Food or additives" revised and announced by MHLW Notice No.0327-2 of March 27, 2015.
- Japanese Ministry of Health, Labor and Welfare - Notification No. 210 of the MHLW issued on May 20, 2003 and the latest version by Notification No. 1002-27 about the partial amendment of the criteria eliminating source country restrictions, applicable from November 25th 2014.

  Capsugel bovine bone gelatin suppliers certify vertebrae removal independent from the age of the animals.

- The raw material is derived from healthy animals slaughtered in a slaughterhouse, which have been inspected by an official veterinarian and have been deemed fit for human consumption.

Capsugel continuously monitors all regulatory activities; please let us know if there are further questions or clarification needed.

For further information, please consult your customer service representative.

Valid as of
September, 2015

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2.1.P.4.6 Novel Excipients

No novel excipients are used in the formulation.

2.1.P.5 Control of Drug Product

2.1.P.5.1 Specifications

Release specifications for Nabilone placebo capsules are presented in the table below.

Test	Specifications	Method
Appearance	Nabilone placebo capsules: Opaque capsules size 4, body white, cap white; filled with a white to slightly yellow powder.	Visual inspection
Identification	It appears as either angular polyhedral granules of irregular sizes with diameters ranging from about 2 µm to about 23 µm or as rounded or spheroidal granules of irregular sizes with diameters ranging from about 25 µm to about 35 µm (see Figure below). The central hilum consists of a distinct cavity or 2- to 5-rayed cleft and there are no concentric striations. Between orthogonally orientated polarising plates or prisms, the starch granules show a distinct black cross intersecting at the hilum.	According to Ph. Eur. monograph 0344 maize starch, identification method A
Uniformity of dosage units	n=10: AV NMT 15.0% n=30: AV NMT 15.0% and no unit less than 0.75 M more than 1.25 M	Ph. Eur. 2.9.40
Dissolution time	Start of content release ≤ 15 min	DAC Probe 13
Microbiological quality TAMC TYMC *E.Coli*	 NMT 10^3 CFU/g NMT 10^2 CFU/g Absent in 1 g	 Ph. Eur. 2.6.12 Ph. Eur. 2.6.13

2.1.P.5.2 Analytical Procedures (Nabilone, 1 mg and 0.25 mg capsules)

The analytical procedures used to analyse Nabilone capsules are listed in the table below. A description of the in-house methods is provided on the following pages.

Test	**Method**
Appearance	Visual inspection
Identification	According to Ph. Eur. monograph 0344 maize starch, identification method A
Uniformity of dosage units	Ph. Eur. 2.9.40 (Mass uniformity)
Dissolution time	DAC Probe 13
Microbiological quality TAMC / TYMC *E.Coli*	 Ph. Eur. 2.6.12 Ph. Eur. 2.6.13

2.1.P.5.2.1 Appearance

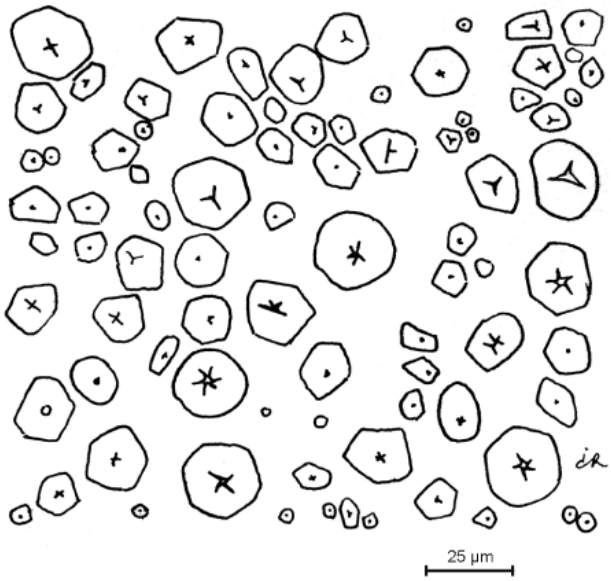
Visual inspection

2.1.P.5.2.2 Identification

The test is performed according to Ph. Eur. monograph 0344 maize starch, identification method A.

The content of 1 capsule is suspended using a 50 per cent V/V solution of glycerol R and examined by microscope.

It appears as either angular polyhedral granules of irregular sizes with diameters ranging from about 2 µm to about 23 µm or as rounded or spheroidal granules of irregular sizes with diameters ranging from about 25 µm to about 35 µm (see Figure below). The central hilum consists of a distinct cavity or 2- to 5-rayed cleft and there are no concentric striations. Between orthogonally orientated polarising plates or prisms, the starch granules show a distinct black cross intersecting at the hilum.



2.1.P.5.2.3 Uniformity of dosage units

The test is performed according to Ph. Eur. 2.9.40. Mass uniformity is applied as the capsule contains only one ingredient and no active.

2.1.P.5.2.4 Dissolution time

The test is performed according to DAC Probe 13 (Deutscher Arzneimittel-Codex).

DAC-Probe 13

Zerfallszeit von Kapseln

Vorprüfung: In sechs 100-ml-Erlenmeyerkolben werden jeweils 50 ml Wasser R eingefüllt und auf 37 ± 2 °C temperiert. In die Kolben wird jeweils eine Kapsel gegeben, wobei die Formlinge möglichst nicht an der Glaswand ankleben sollten. Aufschwimmende Kapseln werden mit einem Stück eines indifferenten Materials, zum Beispiel einer aus wenigen Windungen bestehenden Drahtspirale, beschwert. Die Kolben werden in Abständen von etwa 1 min schwach umgeschwenkt. Der Beginn der Freigabe des Füllgutes muss innerhalb von 15 min erfolgen.

Bei negativem Ausfall der Vorprüfung ist die Hauptprüfung durchzuführen. Das Ergebnis der Hauptprüfung ist entscheidend.

Hauptprüfung – Zerfallszeit von Tabletten und Kapseln (2.9.1): Die Kapseln müssen den in der Monographie „Kapseln" (Ph. Eur.) für „Hartkapseln" genannten Forderungen entsprechen.

2.1.P.5.2.5 Microbiological Quality (TAMC, TYMC, *E. Coli*)

The tests are carried out according to Ph. Eur. 2.6.12 and Ph. Eur. 2.6.13.

2.1.P.7 Container Closure System

The packaging for the investigational medicinal product consists of the following components:

- a round plastic container with a threaded neck made of white high-density polyethylene (HDPE) and a nominal capacity of 50 mL
- a round plastic child-resistant tamper-evident screw cap made of polypropylene (PP) with a mounted desiccant (2 g silica gel)

All components conform to the current requirements of food and medicinal products packaging.

The following incoming testing of the primary packaging materials is applied by the drug product manufacturer:

Specification for Duma Twist-Off 50 mL Bottles

Test	**Specifications**
Type of Container	Duma Twist-Off 50 mL
Appearance	Free from foreign materials, metal residues, soil or dust. No burn marks, cracks or scratches/bubbles.
Colour	White
Dimensions	
Outer diameter	35.2 – 36.2 mm
Height	82.3 – 84.3 mm
Identity	IR-Spectrum must comply with reference spectrum of supplier

Specification for Duma Twist-Off Caps

Test	**Specifications**
Type of Cap	Duma Twist-Off with desiccant insert
Appearance	Free from foreign materials, soil or dust. Desiccant and sealing plate present and fitted correctly
Weight of desiccant	1.8 – 2.2 g
Colour	White
Dimensions	
Outer diameter	35.0 – 36.0 mm
Height	28.7 – 29.5 mm
Diameter inner ring w/o desiccant	18.75 – 19.05 mm
Identity	IR-Spectrum must comply with reference spectrum of supplier

The pack size is 28 capsules per container.

One container together with one patient leaflet is enclosed in a cardboard folding box.

2.1.P.8 Stability

As the Nabilone placebo capsules only contain corn starch, the shelf-life of the capsules is defined with the shelf-life of the corn starch.

To have alignment with the Nabilone study medication, the shelf-life of the placebo capsules is limited to the same retest date as the Nabilone capsules.