INVESTIGATIONAL MEDICINAL DRUG PRODUCT

Quality Part

Ivermectin Placebo tablets

IMPD-006 version: 00

MEDITOP Pharmaceutical Ltd.

02. 2021.

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

1 Products description

The product is presented as follows:

White or almost white, round flat-faced tablet of bevelled edge on both side with marked “32” on one side and with “MSD” on the other side. The dimensions: diameter 5,5 ±0.2 mm and height 1.7-2.3 mm.

2 Composition

The composition of tablets, the quality standard and the role of ingredients are shown in the following tables:

Material	Quantity (mg)	Function	Quality
Excipients of tablet			
Microcrystalline Cellulose	56.01	diluent	Ph.Eur.
Corn Starch, pregelatinized	3.00	disintegrant	Ph.Eur.
BonuLac P clear 992.09 MS*	0.42	colorant	Ph.Eur.
Citric acid (anhydrous)	0.36	antioxidant, buffering agent	Ph.Eur.
Magnesium-stearate	0.15	lubricant	Ph.Eur.
Butylated hydroxy anisole	0.06	antioxidant	Ph.Eur.
Nominal weight of tablet	*60.00*		

*In the form of BonuLac P clear 992.09 MS manufactured by Biogrund.
Bonulac P clear 992.09 MS composition:

- 40.0 % Shellac,
- 17.0 % Modified starch, pregelatinized,
- 16.0 % Carboxymethylcellulose Sodium,
- 15.5 %Talcum,
- 5.0 % Triglyceride, medium chain,
- 4.5 % Ammonium hydrogen carbonate,
- 2.0 % Silicon dioxide

3 Description of Accompanying Reconstitution Diluent(s)

Not applicable.

4 Container Closure System

Packaging types:

20 tablets in a labelled PE container closed by PP closure in carton box with leaflet.

Primary Packaging Materials:
- 40 ml HDPE container
- PP cap
- Induction insert

The dehumidification and tamper-evident closing are provided by induction insert.

For detailed information, see in part *2.1.P.7 Container Closure System.*

2.1.P.2 Pharmaceutical Development

1 Development Summary

The pharmaceutical development report summarizes the development work of the Ivermectin placebo tablets. The verum product, the Stromectol 3 mg tablets, was authorized in Netherland by Merck Sharp & Dohm BV.

During the development of the formulation, the fundamental task was to produce placebo tablets indistinguishable from the active ingredient-containing tablets without measurements. Because the verum product contains 3 mg active substance only, it was decided to use a similar placebo composition for direct compression technology. For tableting tools of similar measurements and graves were used, and the blend was colorized to similar color as well.

2 Comparison of the verum and the placebo product

Stromectol 3 mg tablets authorized in Netherland by Merck Sharp & Dohm BV.

Physicochemical Characterization

The physicochemical characterizations of the Stromectol 3 mg tablets and proposed parameters of Ivermectin placebo tablets are summarized in Table 1.

Table 2.1.P.2-1 Physical characterization of the Stromectol 3 mg verum and placebo tablets

Product	Stromectol 3 mg tablets	Ivermectin placebo tablets
Description	Almost white, round, bevelled edge tablets, imprint on one side: “MSD”, and "32" on the other side	Almost white, round, bevelled edge tablets, imprint on one side: “MSD”, and "32" on the other side
Weight	60 mg	60 mg
Diameter	5.5 mm	5.5 mm
Thickness	2.1 mm	2.1 mm

2.1.P.2.1 Components of the verum and placebo tablets

Well-known excipients of Ph. Eur. quality are used in the products.

The tablets have the following excipients:

Product	Stromectol 3 mg tablets	Ivermectin placebo tablets
Ivermectin	yes	no
Microcrystalline cellulose	yes	yes
Pregeletanized starch	yes	yes
Magnesium stearate	yes	yes
Butilhydroxy anisol	yes	yes
Citric acid anhydrous	yes	yes
BonuLac (coloring)	no	yes

The placebo tablets have the following excipients:

1 Microcrystalline Cellulose

Ph. Eur.: Cellulosum microcristallinum
Chemical Name: Cellulose
CAS Registry Number: 9004-34-6
Empirical Formula: $(C_6H_{10}O_5)_n$
Molecular Weight: ≈36 000, where n ≈220.
Functional Category: Adsorbent; tablet and capsule diluent; tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology
Microcrystalline Cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulation. Cellulose, Microcrystalline also has some lubricant and disintegrant properties that make it useful in tableting.

Description
White, odorless, tasteless, crystalline powder composed of porous particles.

Functionality-related characteristic (Particle size distribution)
The type of microcrystalline cellulose is Vivapur 102.
Vivapur 102 is a medium size standard MCC grade, suited for the majority of directly compressible actives. Combines good flow and high compatibility.
Average Particle Size by laser diffraction is 130µm.
The branded type is a guarantee for the proper particle size.

2 Pregelatinized starch

Nonproprietary Names

BP: Pregelatinised starch
PhEur: Amylum pregelificatum
USPNF: Pregelatinized starch

Synonyms

Compressible starch; Instastarch; Lycatab C; Lycatab PGS; Merigel; Pharma-Gel; Prejel;

Sepistab ST 200; Spress; Starch 1500 G;

Chemical Name and CAS Registry Number

Pregelatinized starch [9005-25-8]

Empirical FormulaMolecular Weight

$(C_6H_{10}O_5)_n$ where n = 300–1000.

Pregelatinized starch is a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules and so render the starch flowable and directly compressible. Partially pregelatinized grades are also commercially available. Typically, pregelatinized starch contains 5% of free amylose, 15% of free amylopectin, and 80% unmodified starch. PhEur 2002 (Suppl 4.1) specifies that pregelatinized starch is obtained from maize (corn), potato, or rice starch.

Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

Description

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

Typical Properties

Acidity/alkalinity: pH = 4.5–7.0 for a 10% w/v aqueous dispersion.
Angle of repose: 40.7 ° (6)
Compressibility: see Starch.
Density (bulk): 0.586 g/cm3
Density (tapped): 0.879 g/cm3
Density (true): 1.516 g/cm3
Flowability: 18–23% (Carr compressibility index)(17)
Moisture content: < 7 %
Particle size distribution: 30–150 µm, median diameter 52 µm.
Specific surface area: 0.26 m2/g (Colorcon)

Stability and Storage Conditions

Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

3 Magnesium stearate

Ph. Eur.:	Magnesii stearas
BP:	Magnesium stearate
USPNF:	Magnesium stearate
Chemical Name:	Octadecanoic acid magnesium salt
CAS Registry Number:	557-04-0
Empirical Formula:	$C_{36}H_{70}MgO_4$
Molecular Weight:	591.34
Structural Formula:	$[CH_3(CH_2)_{16}COO]_2Mg$ The Ph.Eur. 2002 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.
Functional Category:	tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.

Description

Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

4 Buthylhydroxy anisol

Nonproprietary Names

BP: Butylated Hydroxyanisole
PhEur: Butylhydroxyanisole
USPNF: Butylated Hydroxyanisol

Synonyms

BHA, Tenox BHA, Nipanox BHA, tercier-butyl-4-methoxyphenol

Chemical Name and CAS Registry Number

2-tert-Butyl-4-methoxyphenol [25013-16-5]

Empirical Formula; Molecular Weight

$C_{11}H_{16}O_2$; 180.25

Functional Category

Antioxidant

Description

Butylated hydroxyanisole occurs as a white or almost white crystalline powder or yellowish-white waxy solid a faint characteristic aromatic odor.

Typical Properties

Density (true): 1.117 g/cm3
Flash point: 130°C
Melting point: 47°C
Solubility: Practically insoluble in water

Stability and Storage Conditions

Exposure to light causes discoloration and loss of activity. BHA should be stored in a well-closed container, protected from light, in a cool, dry place.

5 Citric acid anhydrous

Nonproprietary Names

BP: Citric acid anhydrous
PhEur: Citric acid anhydrous
USP: Citric acid anhydrous

Synonyms

Anhydrous citric acid, acidum citricum anhydricum, citric acid

Chemical Name and CAS Registry Number

2-Hydroxy-1,2,3-propanetricarboxyic acid; [77-92-9]

Empirical Formula; Molecular Weight

$C_6H_8O_7$; 192.12

Functional Category

Acidifying agent, antioxidant, chelating agent, preservative.

Description

Anhydrous citric acid occurs as colorless or translucent crystals, or a white crystalline powder. It is odorless and has a strong acidic taste.

Typical Properties

Density (true): 1.542 g/cm3
Acidity: pH 2.2 (1 % aqueous solution)
Melting point: 153°C
Solubility: Soluble 1 in 1 of water and ethanol (95%)

Stability and Storage Conditions

The bulk material should be stored in airtight container in a cool, dry place.

6 Bonulac P clear 992.09 MS

Bonulac P clear is a coating material manufactured by Biogrund GmbH which was used in quantity of 0,7 % for colouring the blend for tabletting.

Bonulac P clear 992.09 MS consists of

- 40.0 % Shellac,
- 17.0 % Modified starch, pregelatinized,
- 16.0 % Carboxymethylcellulose Sodium,
- 15.5 %Talcum,
- 5.0 % Triglyceride, medium chain,
- 4.5 % Ammonium hydrogen carbonate,
- 2.0 % Silicon dioxide

All components are Ph. Eur. quality.

2.1.P.2.2 Finished Product

2.1.P.2.2.1 Formulation Development

The composition and specification of the placebo product was developed by MEDITOP Pharmaceutical Ltd. therefore the formulation development was subject of a study as such.

The experiments were made at laboratory scale using the following equipment:

- Hand sieve with 0.8 mm mesh size
- ProCepT 4m8 high shear mixer
- Wynka Kompressor Developer rotating tableting machine with round, flat beveled edge punches (5.5 mm diameter) and marked MSD on the upper punch and 32 on the lower punch. The design of the punches was prepared according to the appearance of the verum tablets. The exact, detailed design was made by the experts of the manufacturer of the punches (I Holland Ltd.).

The following properties of the product were tested:

Blend:

- flowability of the final blend by funnel equipped with an orifice of 10 mm and 15 mm diameter
- bulk density and tapped density

Tablets

- appearance (color, notice defects like capping, lamination, sticking, etc.)
- average mass
- mass variation
- height
- hardness
- friability
- disintegration time

Based on the literature data the following composition is applied for Ivermectin placebo tablets.

Table 2.3.P.2-2 Composition of Ivermectin placebo tablets

Material	**Quantity (mg/tablet)**	
Product	Starting composition	Final composition
Microcrystalline cellulose	48.00	56.01
Pregeletanized starch	10.98	3.00
Butilhydroxy anisole	0.06	0.06
Citric acid anhydrous	0.36	0,36
Magnesium stearate	0.60	0.15
BonuLac (coloring agent)	--	0.42
Nominal weight of tablets	60.00	60.00

The composition of the blends and the property of placebo tablets is summarized in the following table. This composition was made at laboratory scale, size of the batch was 2000 pcs of tablets.

Composition	**Quantity (g/batch)**			
	VAXX056		**VAXX060**	
Microcrystalline cellulose	96.00		280.05	
Pregeletanized starch	21.96		15	
Butilhydroxy anisole	0.12		0.3	
Citric acid anhydrous	0.72		1.8	
Magnesium stearate	1.20		0.75	
BonuLac (coloring agent)	--		2.1	
Weight of batch	120.00		300.00	
Parameters of the blend				
Flowability 10mm (s/100g)	30		34	
Flowability 15mm (s/100g)	15		13	
Bulk density (g/100ml)	0,45		0,43	
Tapped density (g/100ml)	0,57		0,54	
Carr index/Hausner ratio	21,4/1,27		19,8/1,25	
Parameters of the tablets	3 kN force	7 kN force	3 kN force	7 kN force
Appearance	appropriate	appropriate	appropriate	appropriate
Average mass (mg)	61.0	61,7	59,9	60
Weight variation (%)	0.68	0,62	0,97	1,15
Height (mm)	2.04	2,03	1,9	1,86
Hardness (N)	40	34	50	56
Friability (%)	0.26	0,35	-	-
Disintegration time (sec)	19	15	60	80

Conclusion
The results show that the excipients ensure proper parameters of the final blend.
The starting composition gave tablets which were whiter than the Stromectol tablets themselves, therefore 0,7 % BonuLac coating material was blended it as coloring agent. Because at higher compressing force the hardness of the tablets decreased, the quantity of Starch 1500 and magnesium stearate was decreased in the composition.
The final composition gave very similar color to the Stromectol 3 mg tablets and the usual compactibility behavior: hardness is increased by higher force.
According to the result the parameters of placebo blend and tablets fulfil the requirements therefore this composition was chosen for preparation of Ivermectin placebo tablets of the clinical study.

2.1.P.2.3. Manufacturing Process Development

Since the manufacturing for the clinical batch is not required process validation and the clinical batch manufacturing was made on similar or the same equipment as used for the formulation development, additional manufacturing process development was not carried out.

2.1.P.3.1 Manufacturer

1 Manufacture and testing of the finished product

Name: MEDITOP Pharmaceutical Ltd.

Address: Ady Endre street 1
2097 Pilisborosjenő Hungary

2.1.P.3.2 Batch formula

2.1.P.3.2.1 Batch size

Laboratory batch size of Ivermectin mg placebo tablet is 2 000 tablets;
120 g material.

Pilot scale batch size of Ivermectin placebo tablet is 20 000 tablets;
1 200 g material.

2.1.P.3.2.2 Manufacturing formula

Following compositions were used to produce batches of tablets.

	Laboratory batch	**Pilot batch**
Material	**Quantity per batch (g)**	**Quantity per batch (g)**
Microcrystalline Cellulose	112.02	1120.2
Corn Starch, pregelatinized	6.00	60.0
BonuLac P clear 992.09 MS*	0.84	8.4
Citric acid (anhydrous)	0.72	7.2
Magnesium-stearate	0.30	3.0
Butylated hydroxy anisole	0.12	1.2
Nominal weight	**120.00**	**1200.0**

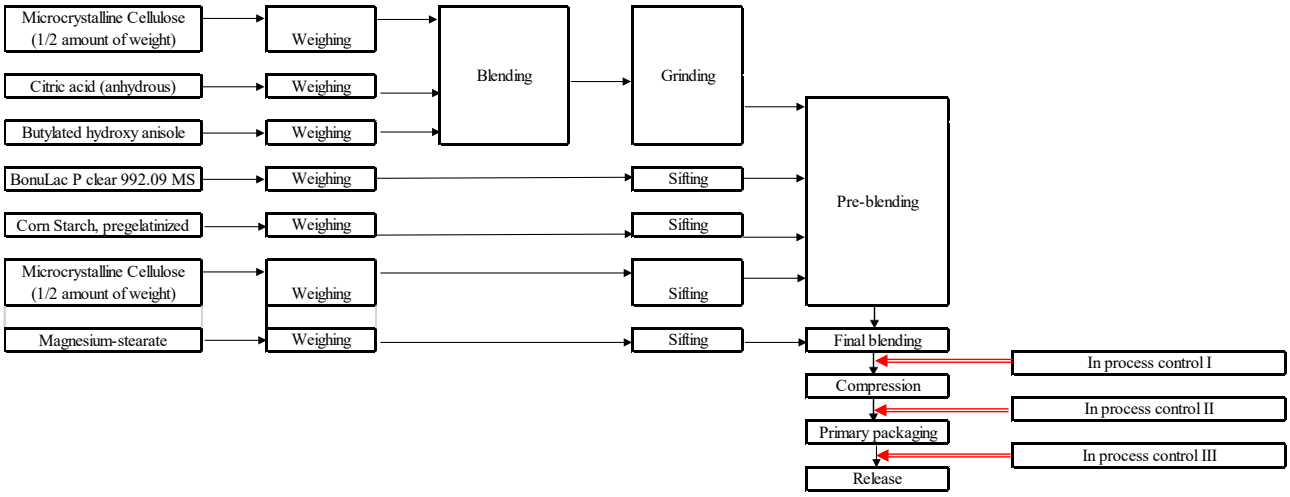
*In the form of BonuLac P clear 992.09 MS manufactured by Biogrund.
Bonulac P clear 992.09 MS composition:

- 40.0 % Shellac,
- 17.0 % Modified starch, pregelatinized,
- 16.0 % Carboxymethylcellulose Sodium,
- 15.5 %Talcum,
- 5.0 % Triglyceride, medium chain,
- 4.5 % Ammonium hydrogen carbonate,
- 2.0 % Silicon dioxide

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

The manufacturing of Ivermectin placebo tablets consist of weighing, grinding, shifting, blending, and compression steps. A description of the manufacturing process is provided below along with a flow chart of the process.

1 Flow chart



2 Weighing of materials

Equipment: Mettler Toledo PUA579
or equivalent equipment

The prescribed amount of core materials of a batch is weighed on the above-mentioned scales into plastic containers lined with polyethylene bags and signed in accordance with the GMP prescriptions.

Measured amount are the followings:

Pilot scale	
Component	**Quantity (g/batch)**
Microcrystalline Cellulose [1]	1176.2
Corn Starch, pregelatinized	60.0
BonuLac P clear 992.09 MS*	8.4
Citric acid (anhydrous) [2]	7.9
Magnesium-stearate	3.0
Butylated hydroxy anisole [2]	1.3

Excipients for grinding:	**Quantity (g/batch)**
Microcrystalline Cellulose [1]	616.1
Citric acid (anhydrous) [2]	7.9
Butylated hydroxy anisole [2]	1.3
Nominal weight:	625.3

[1] + Half of the total amount of microcrystalline cellulose is used for grinding, thus this part is contained +10% overage due to the material lost at the grinding process
[2] + 10% overage due to the material lost at the grinding process

3 Blending

3.1. Grinding

Equipment: Fitzmill M5A comminuting machine
or equivalent equipment

The 616 g of microcrystalline cellulose and the total amount of the citric acid (anhydrous) and butylated hydroxy anisole are blended in polyethylene bag and grinded below 0.8 mm of size by comminuting machine by using of the following parameters:

Milling direction: knife-edged
Milling speed: high

569 g of the grist are weighed out. The remaining grist is measured and this type of grist are overwhelmed according to the prescriptions.

The grinded material is collected into plastic containers lined with double polyethylene bags signed in accordance with the GMP prescriptions and weighted.

3.2. Premixing, blending

Equipment: Vibrating sieve
Pharmatech Multiblender (MB100) powder blender 25L
or equivalent equipment

The BonuLac P clear 992.09 MS, Corn Starch (pregelatinized) and the 560 g amount of Microcrystalline Cellulose is sifted by the vibrating sieve through 0.8 mm diameter galvanized steel wire. Then this shifted material is added into the homogenizing tank.
The measured quantity of the grinded material is added to the same homogenizing tank and blended by using of the following parameters:

Blending time: 15 minutes
Blending speed: 25 rpm

3.3. Final blending

Equipment: Vibrating sieve
Pharmatech Multiblender (MB100) powder blender 25L
or equivalent equipment

Weighted amount of Magnesium-stearate is sifted by the vibrating sieve through 0.8 mm diameter galvanized steel wire. This shifted material is added to the 3.2 powder mix into the tank of the homogenizing equipment, and blended by using of the following parameters:

Blending time: 2 minutes
Blending speed: 25 rpm

Final blend is filled into plastic containers lined with polyethylene bags, signed in accordance with the GMP prescriptions and weighted.

4 In process control I. - Blend for compression

Samples are taken from the blend by quality control department for the in process control and tested according to testing instruction and related specification.

5 Tableting

Equipment: Courtoy R 190 Tablet Press
Courtoy Performa P Tablet Press
Wynka Kompressor Developer Tablet Press
or equivalent equipment

The released blend is sucked by powder intake system into the cone feeder and compressed on Courtoy R 190 Rotary Tablet Press, Courtoy Performa P Tablet Press or Wynka Kompressor Developer Tablet Press. Adequate operation of the metal detector is checked before the tablet making.

The details of the tableting process are the following:

Tableting parameter	**Set value**
Punch diameter	5.5 mm, round flat-faced tablet of bevelled edge on both side
Punch sign	Upper punch: marked "32" Lower punch: marked “MSD”
Average mass	60.0 mg ±10 %
Minimum hardness	25 N
Height	1.7 – 2.3 mm

After setting the compressing machine tablet sample is taken and controlled by the quality control department. If the results fulfil the specifications the tableting process is permitted.

During the tableting process the appearance, weight, hardness and height of tablets are controlled with half hour periodicity by the machine operator and with one hour periodicity by the Quality Control.

The tablets are filled into plastic boxes lined by polyethylene bag of tare weight and the gross weight is weighed. The net weight of the tablets is calculated.

6 In-process Control II. - Tablets

After tableting tablet sample is taken by quality control department for the in process control and tested according to testing instruction and related specification.

7 Packaging

7.1 HDPE bottle:

Equipment: Counter machine
Capping machine
equivalent equipment

Preparation of primer packaging

Primer packaging materials are inspected by QC. It must not be used any packaging materials if the foil package is torn or the foil is damaged.

Filling details: 20 pieces tablets / bottle

Unit number: According to the prescription of clinical study protocol.

Labelling: According to the prescription of clinical study protocol.

20 tablets in a labelled PE container closed by PP closure in carton box with leaflet.

Primary Packaging Materials:

- 40 ml HDPE container
- PP cap
- Induction insert

The dehumidification and tamper-evident closing are provided by induction insert.

For detailed information, see in part *2.1.P.7 Container Closure System.*

7.2 In process control III. - Bottles

Samples are taken for in process control under packaging procedure for testing bottle closing.

Pressure to close the vial: The bottles should be closed with sufficient pressure to close the cap properly. The cap closes properly if it cannot be opened without damaging the safety plastic strip.

7.3 Cartoning

There is not any cartooning of the Ivermectin placebo tablet for clinical study.

7.4 In process control IV. - Finished Products

The samples are taken for in process control of packaged product according to Sampling instruction of finished products.

7.5 Collecting

The closed, labelled containers of Ivermectin placebo tablets together with some containers of repacked Stromectol 3 mg tablets are collected in collector boxes according to the randomization protocol of the clinical study.

The collector boxes will be transported to the clinical study centres.

2.1.P.3.4 Control of Critical Steps and Intermediates

1 In-process controls

1.1 In-process control I. – Blend for compression

Tests	*Requirements*
Appearance:	White or almost white powder
Ivermectin content:	No ivermectin content

1.2 In-process control II. -Tablets

Tests	*Requirements*
Appearance:	White or almost white, round flat-faced tablet of bevelled edge on both side with marked “32” on one side and with “MSD” on the other side.
Ivermectin content:	No ivermectin content
Dimensions:	Diameter: 5.5 ± 0.2 mm Height: 1.7 – 2.3 mm
Average mass:	60.0 mg ± 10 %
Uniformity of mass:	18/20 average mass ± 10 % 20/20 average mass ± 20 %
Hardness:	NLT 25 N
Friability:	NMT 1.0 %
Disintegration:	NMT 15 minutes

1.3 In-process control IV. – Bottle closing control

Tests	*Requirements*
Bottle closing	comply

1.4 In-process control V. - Finished product control

During packaging the following items have to be checked:

- Identification of the packaging materials and the product
- Entirety checking of packaging units
- Checking of readability and markings
- Parameter checking of the equipment

Tests	*Requirements*
Finished product	comply

2 Final product control

Stromectol 3 mg placebo tablets are tested according to drug product specifications according to *Section 2.1.P.5.1 Specifications*. The specifications are for release and end of shelf-life.

2.1.P.5.1. Specification

Ivermectin Placebo tablet is tested according to the specification detailed below.

Tests	*Methods*	*Acceptance criteria*	*Frequency*
Appearance	visual	White or almost white, round flat-faced tablet of bevelled edge on both side with marked "32" on one side and with "MSD" on the other side.	every batch
Average mass	*Ph.Eur. [2.9.5]*	60.0 mg ± 10 %	every batch
Uniformity of Mass	*Ph.Eur. [2.9.5]*	Average mass ± 10 % (18/20) Average mass ± 20 % (20/20)	every batch
Hardness	*Ph.Eur. [2.9.8]*	NLT* 25 N	every batch
Dimension - diameter - height	*In-house*	 5.5 mm ± 0.2 mm 1.7 – 2.3 mm	 every batch
Disintegration	*Ph.Eur. [2.9.1]*	NMT* 15 min	every batch

*NMT: Not more than, NLT: Not less than

2.1.P.5.4 Batch of Analyses

1 Description of Batches

Batch No.	Date of Manufacturing	Batch Size (dose units)	Manufacturing site
IP12001	02.2021.	20 000	MEDITOP Pharmaceutical Ltd.

2 Results of Batch Analysis

One batch was tested according to drug product specification.

Tests	Requirements	Results
		IP12001
Appearance	White or almost white, round flat-faced tablet of bevelled edge on both side with marked "32" on one side and with "MSD" on the other side.	complies
Average mass	60.0 mg ± 10 %	58.7 mg
Uniformity of mass	Average mass ± 10 % (18/20) Average mass ± 20 % (20/20)	57.8-59.8 mg
Hardness	NLT* 25 N	35 N 33-37 N
Dimension - diameter - height	 5.5 ± 0.2 mm 1.7 – 2.3 mm	 5.41 1.94
Disintegration	NMT*15 min	0'27"

*NLT: not less than, NMT: not more than