

Certificate No: IT-API/276/H/2023

## CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

### Part 1

#### Issued following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC

The competent authority of Italy confirms the following:

The manufacturer INDENA S.P.A.

Site address Viale Ortles, 12 - 20139 MILANO (MI)

Is an active substance manufacturer that has been inspected in accordance with Art. 111(1) of Directive 2001/83/EC transposed in the following national legislation: **D.L. n. 219 of 24<sup>th</sup> April 2006 art. 53**

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on 2023/07/13, it is considered that it complies with the Good Manufacturing Practice requirements referred to in the principles of GMP for active substances referred to in Article 47 of Directive 2001/83/EC.

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

**Part 2**

**Name and address of the site:**

**INDENA S.P.A. - Viale Ortles, 12, 20139 MILANO (MI)**

Name of the active Substances manufactured or imported:

BETA-ESGIN (Aesculus hippocastanum L., seed) DRY EXTRACT REFINED  
BOLDINE  
MILK THISTLE FRUIT (Silybum Marianum L.GAERTNER) DRY EXTRACT  
COLCHICINE  
CROFELEMER  
DOCETAXEL  
DOCETAXEL TRIHYDRATE  
ENOXOLONE  
GALANTHAMINE HYDROBROMIDE  
ST. JOHN'S WORT FLOWERING TOPS (Hypericum perforatum L.) QUANTIFIED DRY EXTRACT  
BILBERRY FRESH FRUIT (Vaccinium myrtillus L.) DRY EXTRACT STANDARDISED (Ph. Eur.)  
TRITERPENIC MIX FROM CENTELLA ASIATICA LEAF (Centella asiatica (L.) Urban)  
PACLITAXEL (SEMI-SYNTHETIC)  
PACLITAXEL FROM WHOLE PLANT  
PANAX GINSENG ROOT (Panax Ginseng C.A. Meyer) DRY EXTRACT  
PENTOSAN POLYSULFATE SODIUM  
RESERPINE  
RUSCOGENINS  
SAW PALMETTO FRUIT (Serenoa repens (W. Bartram) Small) soft extract  
THIOLCHICOSIDE  
THIOLCHICOSIDE (BY FERMENTATION)  
THIOLCHICOSIDE (SEMI-SYNTHETIC)  
THIOTEPA

### 3 - Manufacturing Operations - Active Substances

#### BETA-ESCIN (*Aesculus hippocastanum* L., seed) DRY EXTRACT REFINED

3.5	General Finishing Steps
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### BOLDINE

3.5	General Finishing Steps
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### MILK THISTLE FRUIT (*Silybum Marianum* L.GAERTNER) DRY EXTRACT

3.5	General Finishing Steps
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p>

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 GMP Inspections and Manufacturing Authorizations of APIs Office  
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 website: [www.agenziafarmaco.it](http://www.agenziafarmaco.it)  
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CV  
GMP

Page 3

**3.5.3.** Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)

### 3 - Manufacturing Operations - Active Substances

#### COLCHICINE

<b>3.5</b>	<b>General Finishing Steps</b>
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### CROFELEMER

<b>3.5</b>	<b>General Finishing Steps</b>
	<p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### DOCETAXEL

<b>3.5</b>	<b>General Finishing Steps</b>
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**3.5.2.** Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)  
Special Requirements  
Other: Cytotoxic

**3.5.3.** Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)

### 3 - Manufacturing Operations - Active Substances

#### DOCETAXEL TRIHYDRATE

3.5	General Finishing Steps
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) Special Requirements Other: Cytotoxic</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### ENOXOLONE

3.5	General Finishing Steps
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### **GALANTHAMINE HYDROBROMIDE**

<b>3.5</b>	<b>General Finishing Steps</b>
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### **ST. JOHN'S WORT FLOWERING TOPS (*Hypericum perforatum* L.) QUANTIFIED DRY EXTRACT**

<b>3.5</b>	<b>General Finishing Steps</b>
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### **BILBERRY FRESH FRUIT (*Vaccinium myrtillus* L.) DRY EXTRACT STANDARDISED (Ph. Eur.)**

<b>3.5</b>	<b>General Finishing Steps</b>
	<b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a

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Page 6

packaging material which is in direct contact with the substance)  
**3.5.3.** Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)

### 3 - Manufacturing Operations - Active Substances

#### TRITERPENIC MIX FROM CENTELLA ASIATICA LEAF (Centella asiatica (L.) Urban)

##### 3.5 General Finishing Steps

**3.5.2.** Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)  
**3.5.3.** Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)

### 3 - Manufacturing Operations - Active Substances

#### PACLITAXEL (SEMI-SYNTHETIC)

##### 3.5 General Finishing Steps

**3.5.2.** Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)  
Special Requirements  
Other: Cytotoxic  
**3.5.3.** Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)

### 3 - Manufacturing Operations - Active Substances

#### PACLITAXEL FROM WHOLE PLANT

3.5	General Finishing Steps
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) Special Requirements Other: Cytotoxic</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### PANAX GINSENG ROOT (Panax Ginseng C.A. Meyer) DRY EXTRACT

3.5	General Finishing Steps
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### PENTOSAN POLYSULFATE SODIUM

3.5	General Finishing Steps
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a</p>



packaging material which is in direct contact with the substance)  
**3.5.3.** Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)

### 3 - Manufacturing Operations - Active Substances

#### RESERPINE

3.5	General Finishing Steps
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### RUSCOGENINS

3.5	General Finishing Steps
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### SAW PALMETTO FRUIT (*Serenoa repens* (W. Bartram) Small) soft extract

3.5	General Finishing Steps
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### THIOLCHICOSIDE

3.5	General Finishing Steps
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### THIOLCHICOSIDE (BY FERMENTATION)

3.5	General Finishing Steps
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an</p>

outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)

### 3 - Manufacturing Operations - Active Substances

#### THIOLCHICOSIDE (SEMI-SYNTETHIC)

3.5	General Finishing Steps
	<p><b>3.5.2.</b> Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p> <p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

### 3 - Manufacturing Operations - Active Substances

#### THIOTEPA

3.5	General Finishing Steps
	<p><b>3.5.3.</b> Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)</p>

## Restrictions or clarifying remarks:

The active substances can be manufactured at different concentrations and using different extraction solvents. On a risk-based approach, the validity of the GMP certificate for this manufacturing site is not more than 42 months from the latest general GMP inspection conducted on 2023/07/13, except for AIFA's re-evaluation of the risk profile

Rome, 2023/11/24

**Name and signature of the authorised person of  
the Competent Authority of Republic of Italy**

Dott. Michele Marangi  
*AIFA - GMP Inspections and Manufacturing  
Authorizations of APIs Office*

Electronically signed according to the Italian legislation

***Stamp duty paid according to the current Italian legislation.***