Substance Names, Mandatory Sources and Standardization

ISO/ FDIS-IDMP DATABASE 11238

CBG-MEB: Department of Substances

Herman Diederik and Ciska G. Matai

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COLLEGE
TER BEOORDELING VAN
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MEDICINES
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BOARD

Mandatory Sources: Europe:

A: **DIRECTIVE 2001/83/EC** of the European Parliament Relating to Medicinal Products for Human Use, as amended.

TITLE I: Provides Definitions for:

- Medicinal Product; Substance; Immunological medicinal product;
- Homeopathic medicinal product;
- Radiopharmaceutical, Radionuclide generator, Kit, Radionuclide precursor;
- Medicinal products derived from human blood
- Traditional- and herbal medicinal product; herbal substances and preparations;
- **Common name:**
  The international non-proprietary name recommended by the World Health Organization, or, if one does not exist, the usual common name.

- TITLE II: *Article 11:* **Description of content of the Summary of the Products Characteristics *(SPC)***

Mandatory Sources: Europe:

- Description of content of the Summary of the Products Characteristics ***(SPC)*****: section 1, 2 and 6.1:**
- **1.** Name of the Medicinal Product + Strength and Pharmaceutical form;
- **2.** Qualitative and Quantitative composition in terms of the active substance and constituents of the excipient;
- **The usual common name or chemical description shall be used.**
- **6.1** List of excipients;
- **Guidelines,** *f.i.*

  - Guideline on the Chemistry of New Active Substances;(130/96, Rev1)
  - Guideline on Investigation of Chiral Active Substances (3CC29c)
  - Guideline on Pharmaceutical aspects of the Product information for Human Vaccines; (EMA/CPMP/BWP/2758/02)
  - Guideline on Quality of Herbal Medicinal Products, Traditional Herbal Medicinal Products (CPMP/QWP/2819/00 Rev 1)

Connection between Marketing Authorization and the SPC

- Article 8(3)(j) of Directive 2001/83/EC and Article 6(1) of Regulation (EC) 726/2004 require that,

  in order to obtain a marketing authorization,
  a Summary of Product Characteristics (SmPC)
  in accordance with Article 11 of Directive 2001/83/EC
  must be included in the application.

- **For decisions concerning Centralized marketing authorizations**, according to Article 10 of Regulation (EC) no 726/2004, the **final Commission decision with the SmPC is addressed and notified to the Marketing Authorization Holder.**

- **Thus, the SmPC forms an intrinsic and integral part of the marketing authorization.**

The SPC is written in English and translated into the Language of each Member State

SPC: Section 2: QUALITATIVE AND Q UANTITATIVE COMPOSITION

- **Qualitative declaration:**

The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant, or

the European Pharmacopoeial name if that name represents an established name in Europe.

If no INN exists, the European Pharmacopoeia name should be used or if the substance is not in the pharmacopoeia, the usual common name should be used.

In the absence of a common name, the exact scientific designation should be given.
Substances not having an exact scientific designation should be described by a statement on how and from what they were prepared.

SPC: Section 2: QUALITATIVE AND Q UANTITATIVE COMPOSITION

- **Quantitative declaration:**

The quantity of the active substance should be expressed per dosage unit, per unit volume, or per unit of weight and should be related to the declaration of strength in the SPC section 1;

Salts and hydrates

Where the active substance is present in the form of a salt or hydrate, the quantitative composition should be expressed in terms of the mass [or biological activity in International (or other) units where appropriate] of the active moiety (base, acid or anhydrous material), e.g. '60 mg toremifene (as citrate)' or toremifene citrate equivalent to 60 mg toremifene'.

Connection between Naming Active Substance "Dutch name field" and wording in Chapter 2 of SmPC

1. NAME OF THE MEDICINAL PRODUCT

<<Product name>> 2 mg/0.625 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg perindopril tert-butylamine equivalent to 1.67 mg perindopril and 0.625 mg indapamide.

Excipient:
Each tablet contains 33.74 mg lactose.
For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Oblong, white, slightly biconvex tablets with bevelled edges.

Active Substance Representation of Pharm. Product, Tablet

Class: Ingredient

	Property	Value
	Ingredient Type:	Actief bestanddeel
*	Substance:	9999910182 - PERINDOPRIL-TERT-BUTYLAMINE Change Value
	Quantity Value 1:	2,0
	Quantity Operator:	=
	Quantity Value 2:	
	Unit:	mg/stuk Change Value Clear
*	Concerned Pharmaceutical Product:	Co-Tomil 2 mg/0,625 mg, tabletten - 103269 - Tablet Change Value
	Equivalent Substance:	- PERINDOPRIL Change Value
	Equivalent Quantity Value 1:	1,668
	Equivalent Quantity Operator:	=
	Equivalent Quantity Value 2:	
	Equivalent Unit:	mg/stuk Change Value Clear
*	Composition Group:	Samenstelling
	Notes:	

Connection between Naming Active Substance "Dutch name field" and wording in Marketing Authorization License

registratienummer	RVG 103269	
naam van het geneesmiddel	Perindopril tert-butylamine/Indapamide 2/0,625 A tabletten 2/0,625 mg	
farmaceutische vorm	Tablet	
werkzame stoffen en hoeveelheid per doseringseenheid of de concentratie	INDAPAMIDE 0-WATER	0.625 mg/stuk
	PERINDOPRIL-TERT-BUTYLAMINE	2.0 mg/stuk
	OVEREENKOMEND MET PERINDOPRIL	1.668 mg/stuk
naam en adres houder van de handelsvergunning	Apothecon B.V. Nijverheidsweg 3 3771 ME Barneveld	
datum van afgifte	6 april 2009	
datum van verlenging voor onbepaalde tijd	11 januari 2012	
afleverstatus	Uitsluitend recept	
wettelijke grondslag	Art 10(1), Directive 2001/83/EC, generic application	

Utrecht, 02 augustus 2012

Deze pagina('s) vormt (vormen) samen met de laatst goedgekeurde versie van de samenvatting van de productkenmerken de handelsvergunning.

MANDATORY SOURCES

What do we understand with a “Common Name”

The information on the nomenclature of a substance should be provided, if relevant by:

- **International Nonproprietary Name (INN) or Recommended INN** and are assigned by the WHO.
  A rule has been established to determine the gender of INN’s in French:
  Names ending in “–one” or “-ine” are feminine and all the others are masculine.
- Salts en Esters: When an INN is assigned to a particular salt or ester (f.i levothyroxine sodium), the name of the acid or the base, or that of another salt or ester, may be chosen as a modified (INNm) (Levothyroxine) derived from the recommended INN.
- Substances not covered by INNs:
  mixtures of substances; substances not completely characterized; herbal substances; substances having a well-established name (alkaloids).

MANDATORY SOURCES
What do we understand with a “Common Name” (2)

- Compendial Name [e.g.European Pharmacopoeia (EP); United States Pharmacopoeia (USP)]
- National Approved Names:
  BAN, USAN, JAN, Company or Laboratory code
- Systematic Chemical Name(s) (IUPAC nomenclature)
- Other Names (e.g. Proprietary) and Other non-proprietary name(s)
- Chemical Abstract Service (CAS) registry number and
  CAS-Index name.

PREFERRED NAME: <=> TEMPORARY PRIMARY NAME or
<=> PRIMARY APPROVED NAME
<=> Parent SUBSTANCE ISO-IDMP-ID

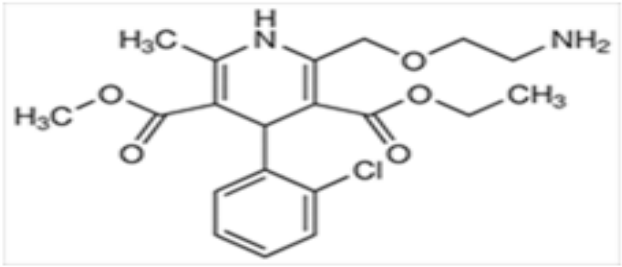
USP: AMLODIPINE BESYLATE; EP: AMLODIPINE BESILATE;

INN: Amlodipini Besilas [rINNM (la)

INN: Amlodipine Besilate [rINNM (en)]

INN: Besilato de amlodipino [rINNM (es)]

INN: Амлодипина Безилат [rINNM (ru)]



CHEMICAL NAME:

CAS: **3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, benzenesulfonate (1:1) (CA INDEX NAME)**

USP: **3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (±)-, monobenzenesulfonate.**

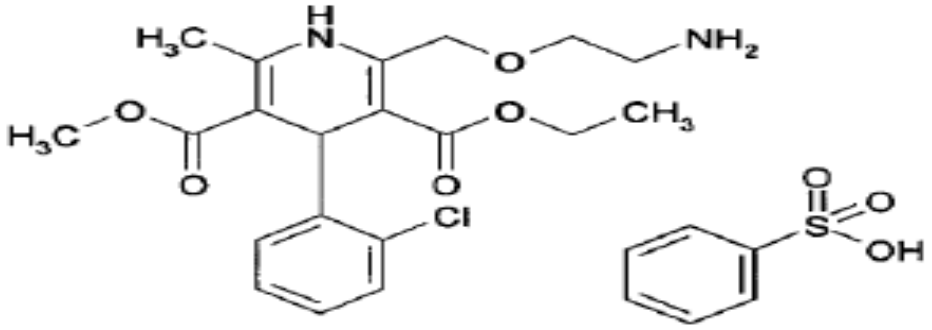
EP: **3-Ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-l,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate.**

Martindale Parent Substance AMLODIPINE:

3-Ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate

APPLICANT:

. Structural formula:



. Molecular formula: $C_{20}H_{25}ClN_2O_5$, $C_6H_6O_3S$

. Relative molecular mass: 567.1 (408.882 + 158.178)
The conversion factor for the salt to the base is 0.721.

. Amlodipine corresponds to the racemic mixture (one asymmetric carbon).

MOLECULAR FORMULA/ Weight:

USP: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$; **567.05**

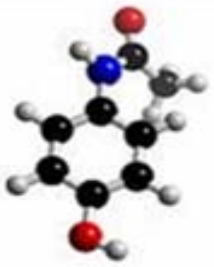
EP: $C_{26}H_{31}ClN_2O_8S$; **567,1**

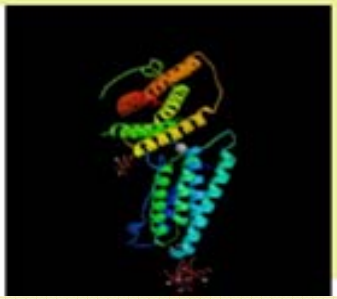
CAS: C20 H25 Cl N2 05 . C6 H6 03 S; No presentation of Mol. Weight.

Martindale: $C_{20}H_{25}ClN_2O_5, C_6H_6O_3S$ **=567.0**

For Non-Stoichiometric Composed Substances and Biological Substances more elements has to be captured:

- Biological medicines produced in a living system or organism
- The (complex) manufacturing process is a determining factor
- Larger molecules, complex (three-dimensional structure) and heterogeneous (e.g. isoforms and multimers)
- Difficult to characterise
- Impurities: Both Product-related and Process-related
- Low stability

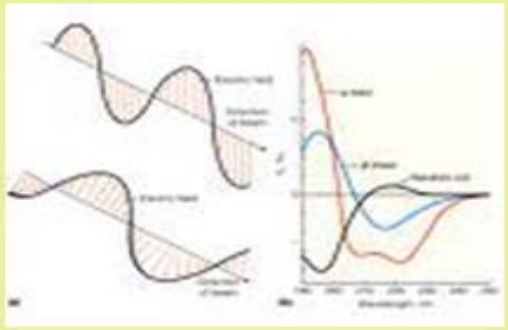


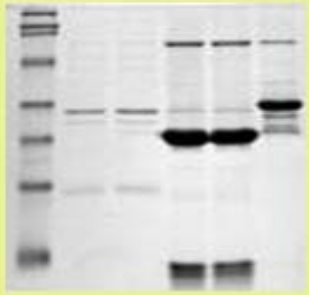


Example: Biosimilar Products

Biosimilar Quality part

- Complete Module 3 (Quality dossier)
- ***Plus* Comparability Excercise**
  - After ***process change*** or ***Biosimilar***
- Reference product
  - Identical primary structure (AA order)
  - Post-translational differences (incl. glycosylation)
  - E.g. Non-PEGylated vs. PEGylated not accepted
- Physicochemical characterisation
- Biological activity
- Impurities
- Stability studies





Example Product Adcetris: Active Substance Brentuximab vedotin

Brentuximab vedotin is a CD30-directed antibody-drug conjugate consisting of 3 components:

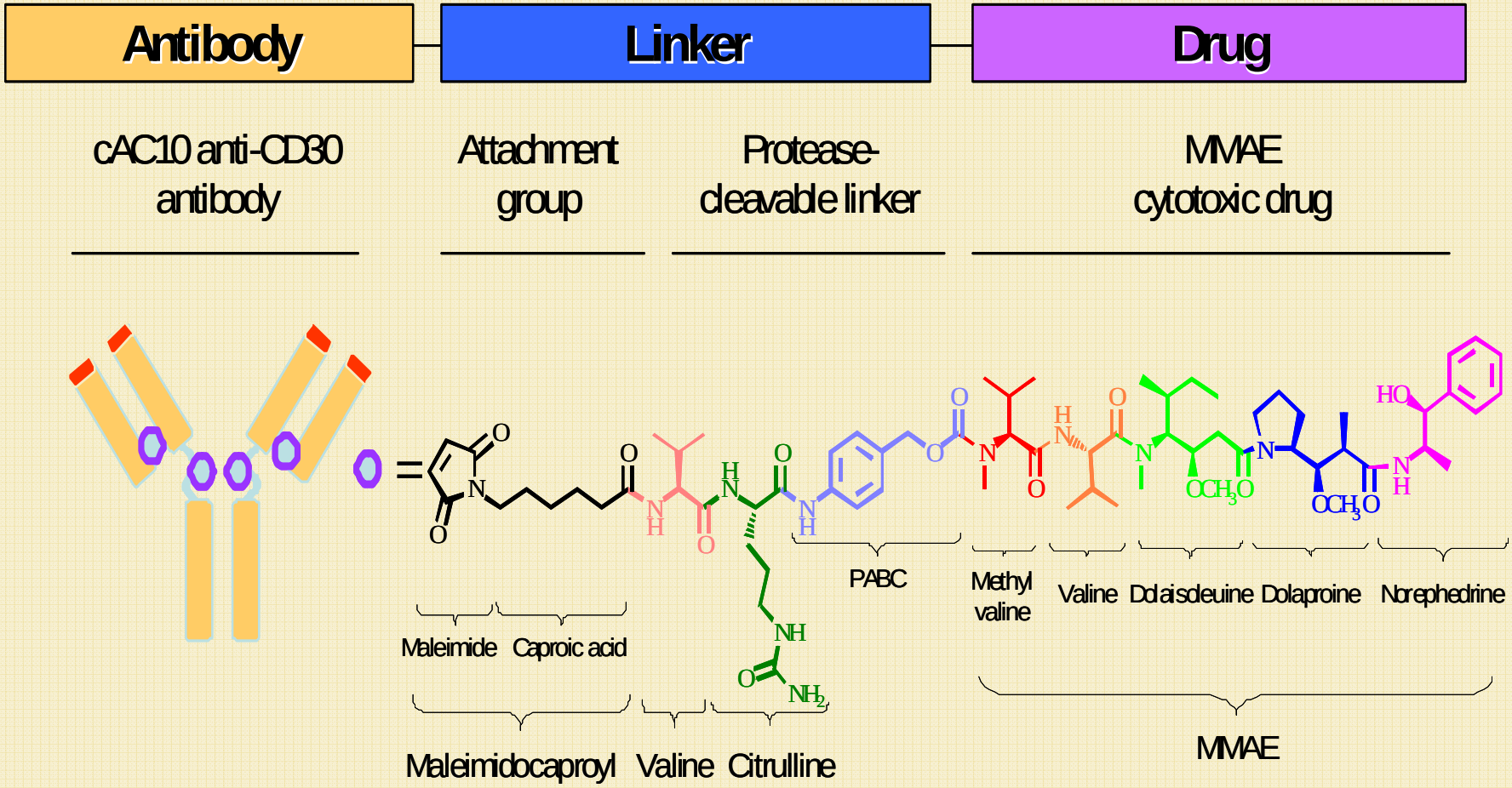
1) The chimeric monoclonal antibody brentuximab, specific for human CD30,
2) The cytotoxic component monomethyl auristatin E (MMAE; and
3) A protease cleavable linker that covalently bonds the cytotoxic component MMAE to the chimeric monoclonal antibody brentuximab. (Structure slide 18)

Chemical name	Code name SGN-35
Molecular formula	$C_{6860}H_{10532}N_{1740}O_{2168}S_{40}$
Molecular weight.	153,352
Cas Register number	914088-09-8

Immunoglobulin G1, anti-(human CD30 (antigen)) (human-mouse monoclonal cAC10 .gamma.1-chain), disulfide with human-mouse monoclonal cAC10 .kappa.-chain, dimer, complex with N-[[[4-[[N-[6-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-1-oxohexyl]-L-valyl-N5-(aminocarbonyl)-L ornithyl]amino]phenyl]methoxy]carbonyl]-N-methyl-L-valyl-N-[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenylethyl]amino]-1-methoxy-2-methyl-3-oxopropyl]-1-pyrrolidinyl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl-L-valinamide

Schematic structure of SGN-35
cAC10 = Recombinant chimeric heterotetramer form (human IgG1) of the murine monoclonal antibody AC10, which is produced by immunizing mice with the CD30-positive large granular lymphoma cell line

MMAE = monomethyl auristatin E, PABC = p-aminobenzylcarbamate; Cas. Reg. no: 914088-09-8



Description of Vaccines in the SPC section 2

(Guideline on Pharmaceutical aspects of the product information for Human Vaccines)

- Qualitative and Quantitative declaration of each active substance
- Qualitative and Quantitative declaration of any adjuvant or absorbent
- A preference to the list of excipients in Section 6.1
- Taxonomic names for cellular microorganism should be captured and the strain, serotype or other appropriate sub-species designation should be included in the name of each antigen, if relevant.
- The nature of any cellular system(s) used for production and if relevant the use of recombinant DNA technology should be mentioned in the SPC.
- The inclusion of a mention of the production process in vaccine active substance names should be restricted to the use of the following terms:

  “Live, attenuated” (for vaccines containing living micro-organisms)

  “Inactivated” (for vaccines containing killed micro-organisms)

Example: *Common EU SPC Batrevac 2012/2013 NL/H*

1.3.1 Harmonised EU-SPC for Influenza vaccines

1. NAME OF THE MEDICINAL PRODUCT

Batrevac 2012/2013, suspension for injection
(influenza vaccine, surface antigen, inactivated).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza virus surface antigens (haemagglutinin and neuraminidase) of the following strains*:

- A/California/7/2009 (H1N1)pdm09-derived strain used (NYMC X-181)	15 micrograms HA **
- A/Victoria/361/2011 (H3N2)-derived strain used (IVR-165)	15 micrograms HA **
- B/Wisconsin/1/2010-like strain used (NYMC BX-39) derived from B/Hubei-Wujiagang/158/2009	15 micrograms HA **
	per 0.5 ml dose

* propagated in fertilised hens' eggs from healthy chicken flocks
** haemagglutinin.

For a full list of excipients see section 6.1.

Batrevac 2012/2013 may contain traces of eggs (such as ovalbumin, chicken proteins), formaldehyde, cetyltrimethylammonium bromide, polysorbate 80, or gentamicin, which are used during the manufacturing process (see section 4.3).

Example: *Common EU SPC Batrevac 2012/2013 NL/H*

Custom Object: **944 - B-WISCONSIN-1-2010-VERWANTE STAM GEBRUIKT (NYMC BX-39) AFGELEID VAN B-Hubei-Wujiagang-158-2009**

Influenza vaccine, split virion, inactivated B-Wisconsin-1-2010- like strain used NYMC BX-39 derived from B-Hubei-Wujiagang-158-2009

1020 - A-CALIFORNIA-7-2009 (H1N1)PDM09-AFGELEIDE STAM GEBRUIKT (NYMC X-181)

"A-CALIFORNIA-7-2009 (H1N1) Like Virus"; "Influenza vaccine, split virion, inactivated A-California-7-2009 (H1N1)pdm09-derived strain used NYMC X-181" Change Value

Quality requirements and naming of Herbal substances

- The quality of herbal medicinal products is determined by the quality of the starting plant material, in-process controls, GMP controls, process validation and by specifications applied to them throughout development and manufacture.
- Consistent quality of products of herbal origin can only be assured if the starting plant material is defined in a rigorous and detailed manner, particularly the specific botanical identification of the plant material used. It is also important to know the geographical source and the conditions under which the herbal substance is obtained in order to ensure that the material is of consistent quality.

Quality requirements and naming of Herbal substances

- The ‘Guideline on Good Agricultural and Collection Practice for starting materials of herbal origin’ provides recommendations for an appropriate quality assurance system on the cultivation and harvesting of plant materials.
- In addition, in accordance with European medicines legislation, the quality dossier should address potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, radioactive contamination, fumigants, etc. Thus, the potential for residues of fumigation agents should be fully considered.

Guideline on Quality of Herbal Medicinal Products/
Traditional Herbal Medicinal Products.
CPMP/QWP/2819/00 Rev 1, EMEA/CVMP/814/00 Rev 1

QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCE(S) OF A HERBAL MEDICINAL PRODUCT

- All herbal substances/herbal preparations are essentially defined by their production process and their specifications;
- Standardized herbal substances/herbal preparations are adjusted to a given content of constituents with known therapeutic activity within an acceptable tolerance; standardization is achieved by adjustment of the herbal substances/herbal preparations with excipients or by blending batches of herbal substances and/or herbal preparations;
- Quantified herbal substances/herbal preparations are adjusted to a defined range of constituents (active markers); adjustment is exclusively achieved by blending batches of herbal substances and/or herbal preparations;
- Other herbal substances/herbal preparations are active substances for which neither constituents with known therapeutic activity nor active markers are known. These herbal substances/herbal preparations are not adjusted to a defined content of analytical marker.

Herbal substances and herbal preparations consisting of comminuted or powdered herbal substances

EXAMPLES

- Active substance

Name: Sennae folium

Quantity: 415-500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as Sennoside B.

- Active substance

Name: Salicis cortex

Quantity: 4 g, corresponding to 40 to 48 mg of total phenolic glycosides, expressed as salicin.

- Active Substance

Name: Valerianae radix 900 mg

673 - HARPAGOPHYTI RADIX, DROOG EXTRACT, ETHANOL-WATER 60 pCt. (1,5-3,0 = 1)

	Property	Value
	CBG Number:	673
	CAS Number:	
*	Dutch Name:	HARPAGOPHYTI RADIX, DROOG EXTRACT, ETHANOL-WATER 60 pCt. (1,5-3,0 = 1)
	Active Ingredient Synonym:	"Dry ethanolic-water 60 pCt. extract obtained from Devil's claw secondary roots."; "Devil¿s claw root consists of the cut and dried, tuberous secondary roots of Harpagophytum procumbens DC. and/or Harpagophytum zeyheri Decne."; "Droog ethanol-water 60 pCt. extract van de Duivelsklauwwortel (H.zeheri Decne en/of H. procumbens D.C.)"; "Droog extract van Windhoek-plantwortel"; "Droog extract van Namibië-plantwortel"
	Origin:	
	Latin Name:	HARPAGOPHYTI EXTRACTUM SICCUM
	INN Name:	HARPAGOPHYTI RADIX, DRY EXTRACT
	English Name:	DEVIL'S CLAW DRY EXTRACT, ETHANOL-WATER 60pCt (1,5-3,0 = 1)
	Inactive Ingredient Name:	
	Notes:	Devil's claw root consists of the cut and dried, tuberous secondary roots of Harpagophytum procumbens DC. and/or Harpagophytum zeyheri Decne. Content: minimum 1.2 per cent of harpagoside (C24H30O11; Mr 494.5) (dried drug). Devil's claw root the characteristic constituents are: Iridoid glucosides, principally harpagoside together with small amounts of harpagide, 8-pcoumaroylharpagide, procumbide and its 6'-p-coumaroyl ester. The phenolic glycosides acteoside (verbascoside) and isoacteoside, and sugars, mainly the tetrasaccharide stachyose with smaller amounts of raffinose, sucrose and monosaccharides are also present. Harpagoside is used as quality marker for both the herbal substance and the herbal preparation. Manufacture: Macerate the roots with 60 pCt. ethanol-water. The macerate is pressed/decanted from the tincture and waisted. The tincture is heated and concentrated and lactose is added. After drying and milling the final extract is achieved.

European Pharmacopoeia

01/2011:1095

DEVIL'S CLAW ROOT

Harpagophyti radix

DEFINITION

Cut and dried, tuberous secondary roots of *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne.

Content: minimum 1.2 per cent of harpagoside ($C_{24}H_{30}O_{11}$; M_r 494.5) (dried drug).

IDENTIFICATION

A. It consists of thick, fan-shaped or rounded slices or of roughly crushed discs. The darker outer surface is traversed by tortuous longitudinal wrinkles. The paler cut surface shows a dark cambial zone and xylem bundles distinctly aligned in radial rows. The central cylinder shows fine concentric striations. Seen under a lens, the cut surface presents yellow or brownish-red granules.

01/2008:1871

DEVIL'S CLAW DRY EXTRACT

Harpagophyti extractum siccum

DEFINITION

Dry extract obtained from Devil's claw root (1095).

Content: minimum 1.5 per cent of harpagoside ($C_{24}H_{30}O_{11}$; M_r 494.5) (dried extract).

PRODUCTION

The extract is produced from the herbal drug by an appropriate procedure using either water or a hydroalcoholic solvent that is at most equivalent in strength to ethanol (95 per cent *V/V*).

Information from the Registration Dossier

3.2.S.1.1 Nomenclature

Definition of the herbal substance:

Binomial scientific name of the plant:	*Harpagophytum procumbens* D.C. and/or *H. zeyheri* L. Decne.
Scientific name of plant:	*Harpagophytum* procumbens D.C. and/or *H. zeyheri* L. Decne.
Synonyms:	Radix *harpagophyti*, tubera *harpagophyti*
German name:	Teufelskrallenwurzel
English name:	Devils`claw root
Parts of the plant:	The dried secondary roots *of harpagophytum procumbens* D.C. and/or *H. zeyheri* L. Decne.

Definition of the herbal preparation:

- Definition of the herbal preparation: Harpagophyti extractum
- Ratio of the herbal substance to the herbal preparation: DER_{native} 1.5 - 3 : 1 referred to the dried drug
- Extraction solvent: Ethanolum 60 % (V/V)

Laboratory code: corresponds Art. No.: 01308200

Information from the Registration Dossier

3.2.S.1.2 Structure

Constituents of the herbal substance:

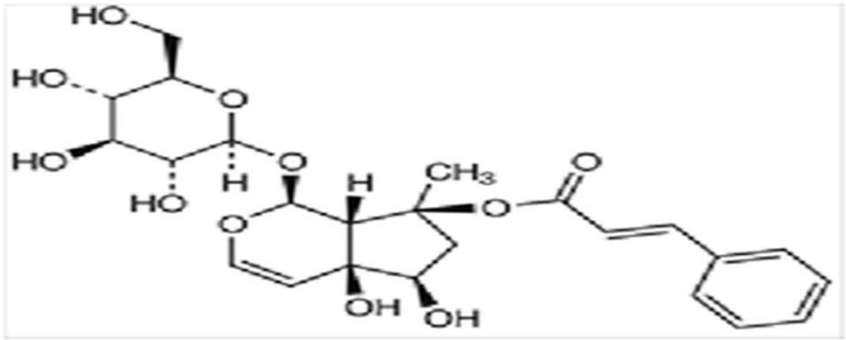
According to ESCOP monograph on Devil's claw root the characteristic constituents are:

Iridoid glucosides, principally harpagoside together with small amounts of harpagide, 8-p-coumaroylharpagide, procumbide and its 6'-*p*-coumaroyl ester. The phenolic glycosides acteoside (verbascoside) and isoacteoside, and sugars, mainly the tetrasaccharide stachyose with smaller amounts of raffinose, sucrose and monosaccharides are also present.

Physical form of the herbal preparation:

The herbal preparation (drug substance) is a fine and hygroscopic powder.

For quantitative determinations (evidence of batch to batch conformity) the marker used is harpagoside (in the herbal substance and in the herbal preparation as well as in the herbal product).



Chemical Structure of Harpagoside

Information from the Registration Dossier

Description of the herbal substance: Harpagophyti radix

According to Ph.Eur.:
Devil's claw root consists of the cut and dried tuberous, secondary roots of *Harpagophytum procumbens* D.C., and/or *H. zeyheri* L. Decne.

It consists of thick, fan-shaped or rounded slices or of roughly crushed discs. The darker outer surface is traversed by tortuous longitudinal wrinkles. The paler cut surface shows a dark cambial zone and xylem bundles distinctly aligned in radial rows. The central cylinder shows fine concentric striations. Seen under a lens, the cut surface presents yellow to brownish-red granules.

Description of the herbal preparation: Harpagophyti extractum

The herbal preparation (drug substance) is a brownish yellow, fine and hygroscopic powder with a light to dark brown colour, odourless and has a bitter taste.

CBG MEB

THANK YOU FOR YOUR ATTENTION

Drs. H. Diederik, Pharmacist
<h.diederik@cbg-meb.nl>

Miss Ing. C.G. Matai, Chemist
<cg.matai@cbg-meb.nl>

Postal address:
P.O. Box 8275,
3503 RG Utrecht,
The Netherlands