Functional Design
ISO/ FDIS-IDMP DATABASE 11238

CBG-MEB: Department of Substances

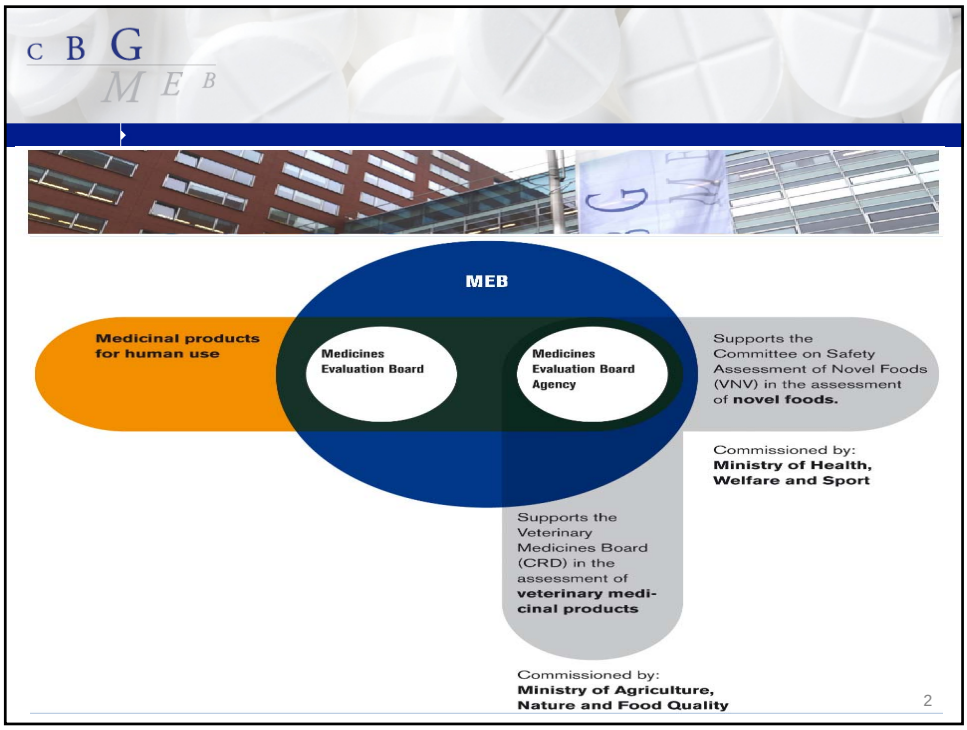
Herman Diederik and Ciska G. Matai

in cooperation with

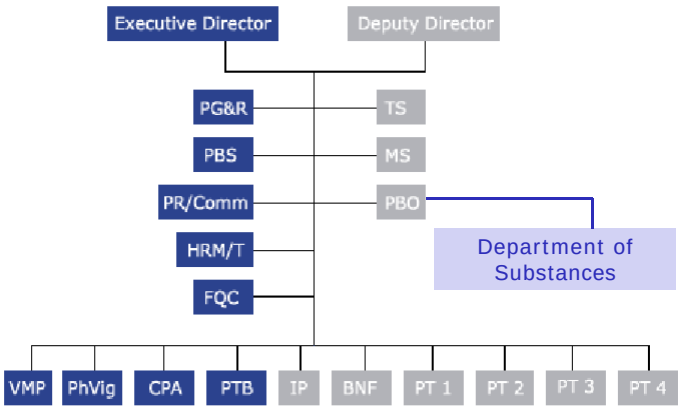
CBG-MEB: Department of Pharmacovigilance
Anja van Haren
CBG-MEB: Department of Int. Affairs/ ICH
Stan van Belkum

February, 2013

COLLEGE TER BEOORDELING VAN GENEESMIDDELEN
CBG MEB
MEDICINES EVALUATION BOARD



ORGANISATION STRUCTURE



3

Current Substance Registration System

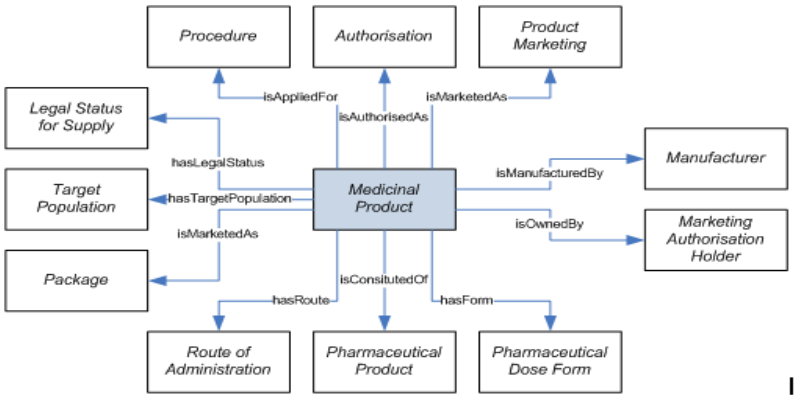


Figure 2-1: Relationships with Medicinal Product Business Concept

4

Current Substance Registration System

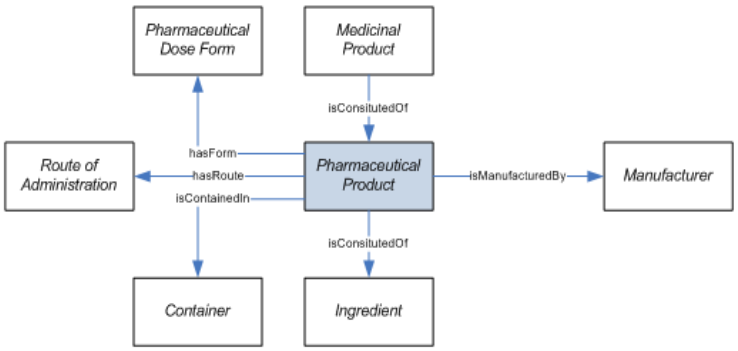


Figure 2-3: Relationships with Pharmaceutical Product Business Concept

5

Current Substance Registration System

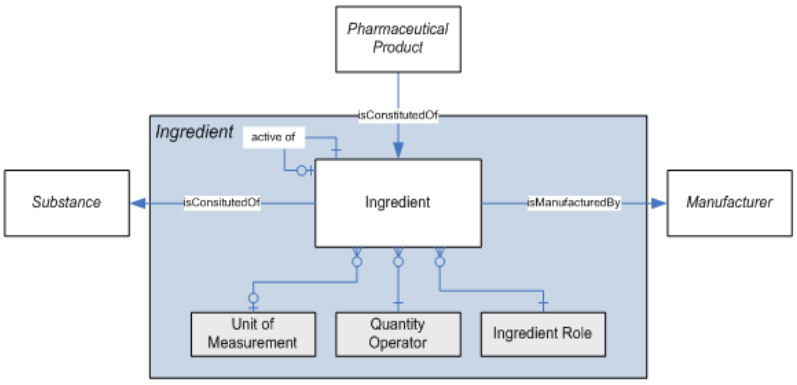


Figure 2-7: Link from Ingredient to Technical Concepts

6

Pharmaceutical Product Representation in “ICI”, Tablet

Filter folder for documents where: Show Advanced Criteria

Document Title contains

Apply Filter Clear

Actions Menu Items Found: 7 View: Detailed Show Items: 500

Title ▲	Quantity Value 1	Quantity Operator	Quantity Value 2	Unit	Ingredient Type	Composition Group
CELLULOSE, MICROKRISTALLIJN					Inactief bestanddeel	Samenstelling
INDAPAMIDE, 0-WATER 0,625 = mg/stuk	0,625	=		mg/stuk	Actief bestanddeel	Samenstelling
LACTOSE 1-WATER					Inactief bestanddeel	Samenstelling
MAGNESIUM STEARATE (E 470B) (RI)					Inactief bestanddeel	Samenstelling
NATRIUMWATERSTOFCARBONAAT					Inactief bestanddeel	Samenstelling
PERINDOPRIL-TERT-BUTYLAMINE 2 = mg/stuk	2,0	=		mg/stuk	Actief bestanddeel	Samenstelling
SILICIUMDIOXIDE (E 551)					Inactief bestanddeel	Samenstelling

7

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:	

8

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.

9

Connection between Naming Active Substance "Dutch name field" and wording in Chapter 6 of Patient Information Leaflet / Package Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER
<<Product name>> 2 mg/0.625 mg tablets
perindopril tert-butylamine/indapamide

Read this leaflet carefully before you start taking this medicine.

6. FURTHER INFORMATION

What <<Product name>> tablets contain

- The active substances are perindopril tert-butylamine and indapamide. Each tablet contains 2 mg perindopril tert-butylamine equivalent to 1.67 mg perindopril and 0.625 mg indapamide.
- The other inactive substances are microcrystalline cellulose, lactose monohydrate, sodium hydrogen carbonate, colloidal anhydrous silica, magnesium stearate.

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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.

11

Active Substance Record Representation

Custom Object: 9999910182 - PERINDOPRIL-TERT-BUTYLAMINE

Close

Class: *Substance (readonly)*

Property	Value
CBG Number:	9999910182
CAS Number:	0107133368
Dutch Name:	PERINDOPRIL-TERT-BUTYLAMINE
Homeopatic Name:	
Preferred Term As Inactive Ingredient:	
Quantity Indicator Inactive Ingredient:	
P RMS:	
Harmonised Substance Data Lock Point:	
Active Ingredient Synonym:	"BUTYL(TERT)AMINOPERINDOPRIL"; "PERINDOPRIL TERT-BUTYLAMINE SALT"; "PERINDOPRILBUTYLAMINE (TERT)"; "S 9490-3"; "TERT-BUTYLAMINOPERINDOPRIL"; "1H-Indole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro(2S,3aS,7aS)-comp.with 2-methyl-2propanamine (1:1)"; "Coversyl"; "2-Methylpropan-2-amine (2S,3aS,7aS)-1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1H-indole-2-carboxylate."; "Perindopril erbumine"
Origin:	
Latin Name:	PERINDOPRILUM TERT-BUTYLAMINUM
INN Name:	PERINDOPRIL-tert-BUTYLAMINE
English Name:	PERINDOPRIL-tert-BUTYLAMINE
Inactive Ingredient Name:	
Notes:	Mol. Gew.: 441,60 Mol. Form.: C19 H32 N2 O5 . C4 H11 N Polymorphism: De stof kan bestaan in een amorfe vorm (Manufactorer LEK) of in diverse crystallijne vormen; Alpha criystallijne vorm: Krka

12

Path: Object Stores > Nice > Medicinal Products > M > ME > Menopur--Dr. Fisher Farma B.V. > Menopur 75 IE, poeder en oplosmiddel voor oplossing voor injectie - 102479 > V004 - Herstelzaak humaan - Approved > Pharmaceutical Products > Poeder voor oplossing voor injectie > Ingredients

Get Info | Bookmark | Add To Shortcuts | Printable View

Filter folder for documents where: | Show Advanced Criteria

Document Title contains

Apply Filter | Clear

Actions Menu | Items Found: 8 | View: Detailed | Show Items: 500

Title	Quantity Value 1	Quantity Operator	Quantity Value 2	Unit	Ingredient Type	Composition Group
FOLLIKEL-STIMULEREND HORMOON 75 = IE/flacon	75,0	=		IE/flacon	Actief bestanddeel	Samenstelling overeenkomend met
LACTOSE 1-WATER					Inactief bestanddeel	Samenstelling
LUTEÏNISEREND HORMOON 75 = IE/flacon	75,0	=		IE/flacon	Actief bestanddeel	Samenstelling overeenkomend met
MENOPAUZEGONADOTROFINE 2000 >= IE/mg	2000,0	>=		IE/mg	Actief bestanddeel	Samenstelling
NATRIUMHYDROXIDE					Inactief bestanddeel	Samenstelling
NITROGEN (HEAD SPACE) (E 941) (RI)					Inactief bestanddeel	Samenstelling
POLYSORBAAT 20					Inactief bestanddeel	Samenstelling
ZOUTZUUR					Inactief bestanddeel	Samenstelling

13

Background

Pharmacovigilance

- Identification of the medicinal product involved in the adverse event report is critical:
  - Specificity within an adverse event/reaction report
  - Clear and accurate communication across jurisdictions (countries & regions)
- More specificity leads to more accuracy in analysis

14
14

European Commission Estimation

- 5% of all hospital admissions due to ADRs
- 5% of all hospital patients experience an ADR
- ADRs 5th most common cause of hospital death
- 197,000 deaths per year in EU caused by ADRs
- Total societal cost €79 billion

ICH Background

ICH M5 Objective:

Develop harmonized standards building on the regulatory and technical processes established in the 3 ICH regions and observer countries

- Standardize terminology/controlled vocabulary concepts and models related to medicinal products
- Standardize the exchange format of regulated medicinal product information

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ISO IDMP Standards (1)

Set of 5 International Standards:

- prEN ISO 11615 Health informatics — Identification of medicinal products - Data elements and structures for the unique identification and exchange of regulated medicinal products

- prEN ISO 11616 Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated pharmaceutical product information

18
18

ISO IDMP Standards (2)

- prEN ISO 11238 Health Informatics — Identification of medicinal products — Data elements and structures Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on substances and specified substances
- prEN ISO 11239 Health Informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging
- prEN ISO 11240 Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of units of measurement

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19

Scope

Together, these five standards:

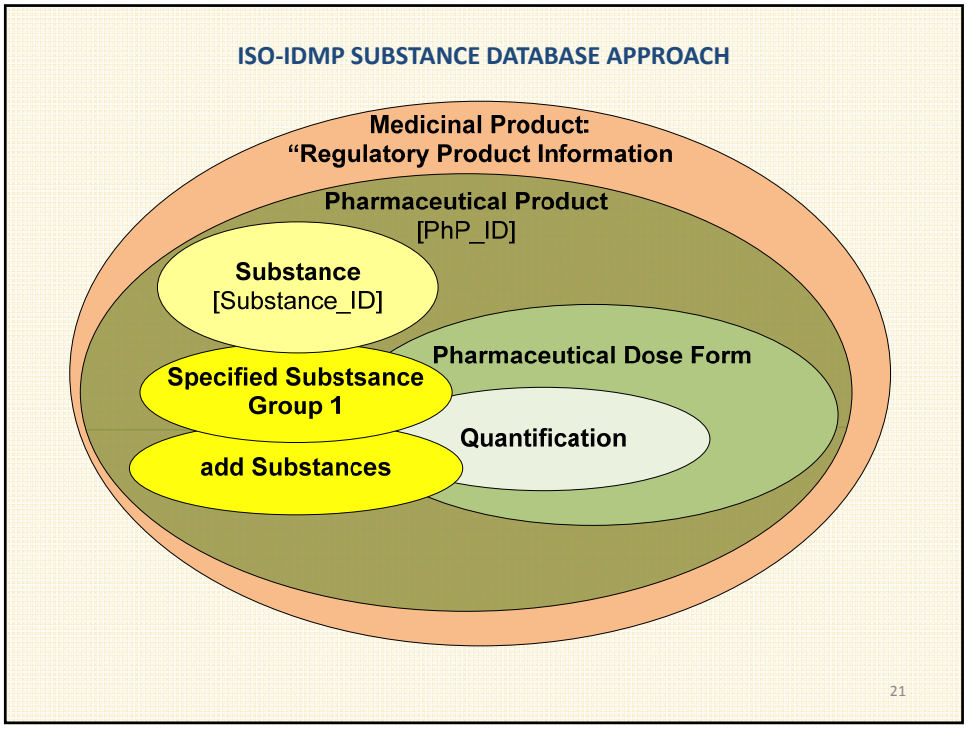
- Define
- Characterize
- Uniquely identify

regulated medicinal products for human use

Support the entire product life cycle management:

- Development
- Authorization (approval)
- Post-marketing
- Renewal or withdrawal as applicable

20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Pharmaceutical Dose Form
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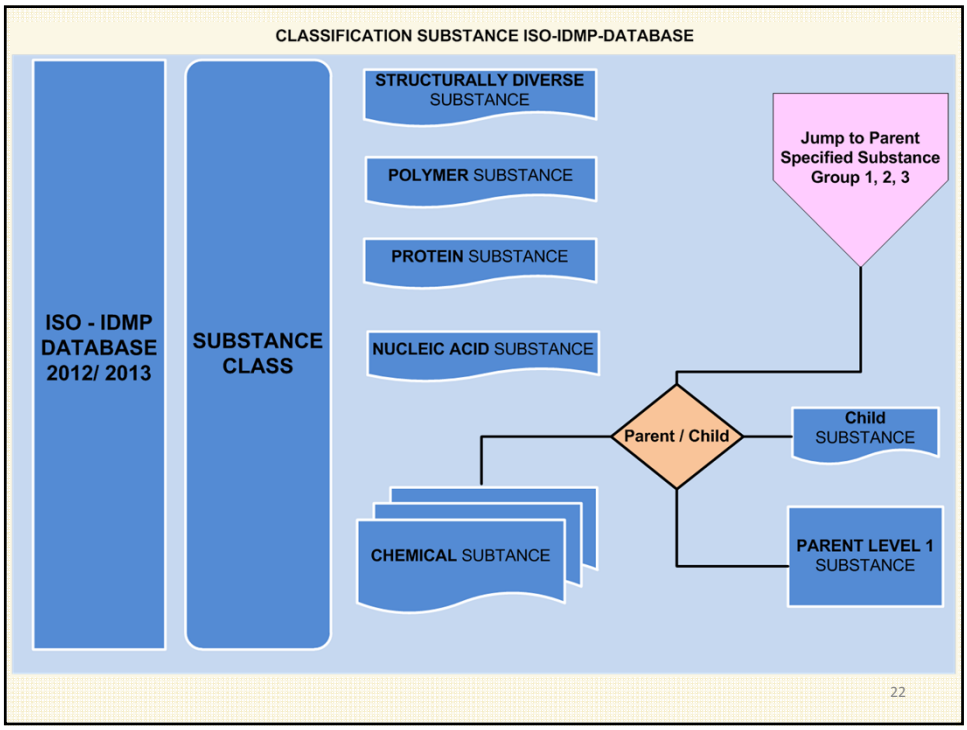
Group 1
Quantification
add Substances
21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ISO - IDMP
DATABASE
2012/ 2013
SUBSTANCE
CLASS
STRUCTURALLY DIVERSE
SUBSTANCE
POLYMER SUBSTANCE
PROTEIN SUBSTANCE
NUCLEIC ACID SUBSTANCE
CHEMICAL SUBTANCE
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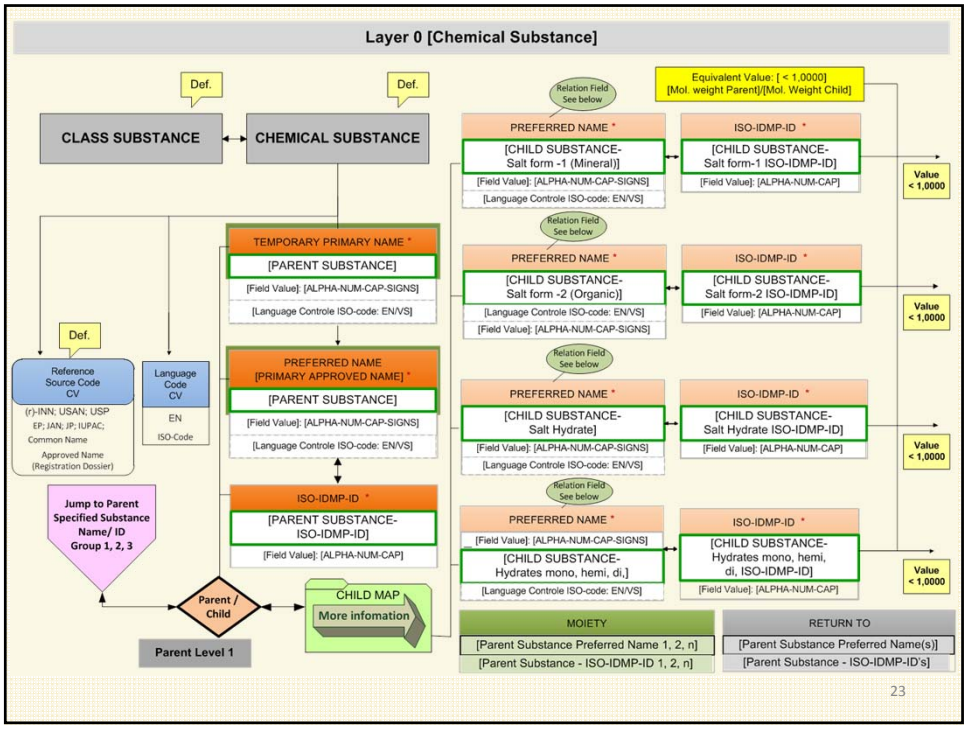
Specified Substance
Group 1, 2, 3
Parent / Child
Child
SUBSTANCE
PARENT LEVEL 1
SUBSTANCE
22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ISO-Code
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More infomation
Parent Level 1
MOIETY
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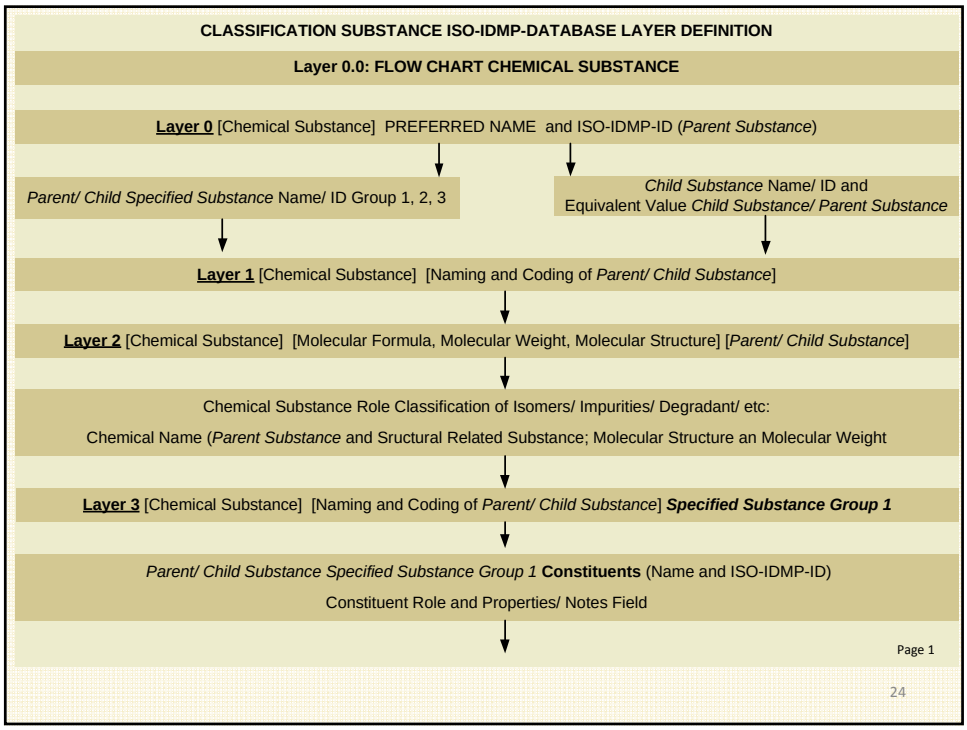
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Child Substance Name/ ID and Equivalent Value Child Substance/ Parent Substance
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Layer 2 [Chemical Substance] [Molecular Formula, Molecular Weight, Molecular Structure] [Parent/ Child Substance]
Chemical Substance Role Classification of Isomers/ Impurities/ Degradant/ etc:
Chemical Name (Parent Substance and Sructural Related Substance; Molecular Structure an Molecular Weight
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Parent/ Child Substance Specified Substance Group 1 Constituents (Name and ISO-IDMP-ID)
Constituent Role and Properties/ Notes Field
Page 1
24

CLASSIFICATION SUBSTANCE ISO-IDMP-DATABASE LAYER DEFINITION *continue*

Layer 4 [Chemical Substance] [Naming and Coding of *Parent/ Child Substance*] or

[Naming and Coding of *Parent/ Child Substance Specified Substance Group 1*]

***Specified Substance* Group 2**

Addition MANUFACTURER(s)

Parent/ Child Substance Specified Substance Group 2 Manufacturer Name and ID-Code

Production Site and GMP Inspection, Inspection date

Layer 5 [Chemical Substance] [Naming and Coding of *Parent/ Child Substance*] or

[Naming and Coding of *Parent/ Child Substance Specified Substance Group 1*]

***Specified Substance* Group 3**

Addition Grade

Type or Description of Grade
Measurement of Technical Grade
Definition of Fineness of Powder
Expression of Particle Size Distribution Specification
Notes Field

Page 2

25

CLASSIFICATION SUBSTANCE ISO-IDMP-DATABASE LAYER DEFINITION *continue*

Layer 6 [*Parent/ Child Substance*] **Documentation**

Public Domain

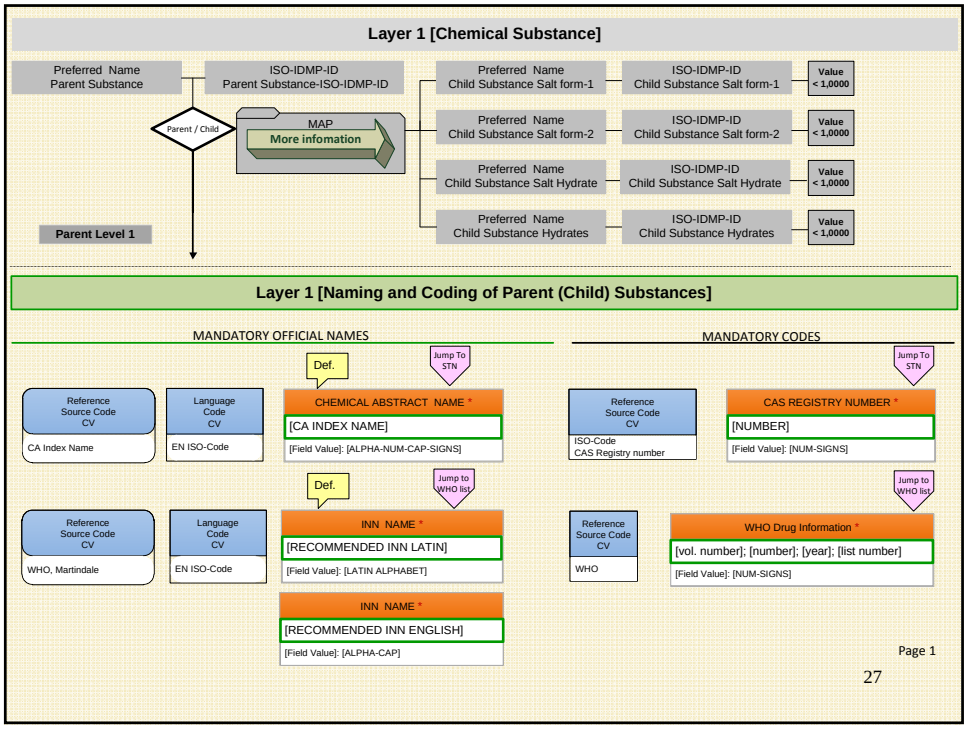
Restricted Domain Part I
(Competent Registration Authority Only)

Restricted Domain Part II
(Competent Registration Authority, Edetorial Reviewer Only)

Layer 7 [Chemical Substance] **LEGEND**

Page 3

26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Parent / Child
MAP
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Value < 1,0000
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ISO-IDMP-ID Child Substance Hydrates
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Page 1
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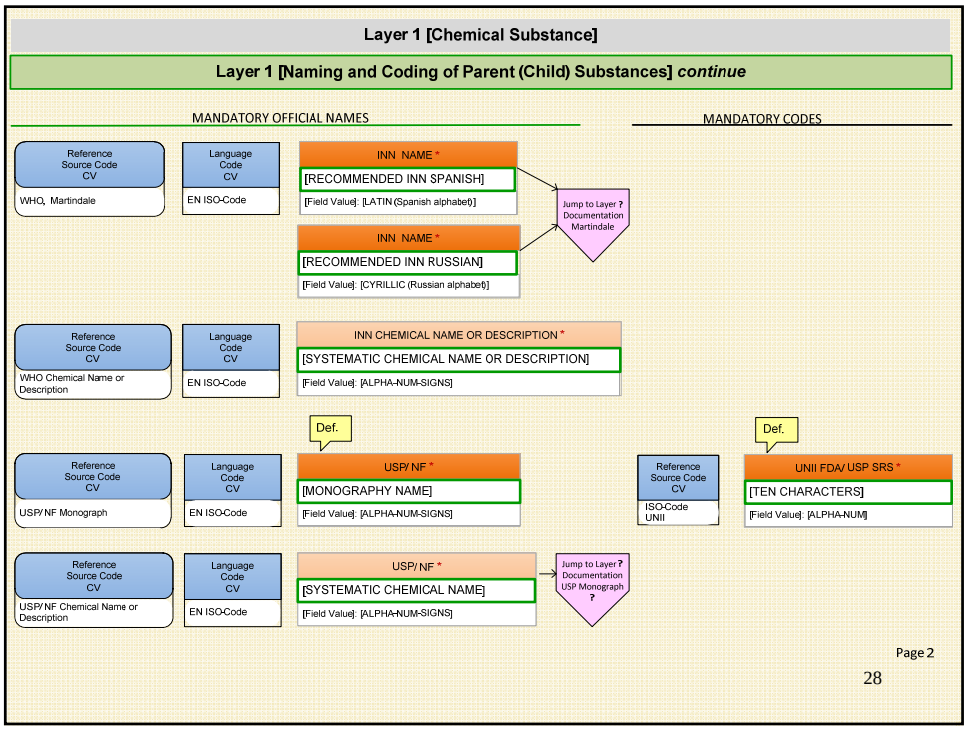
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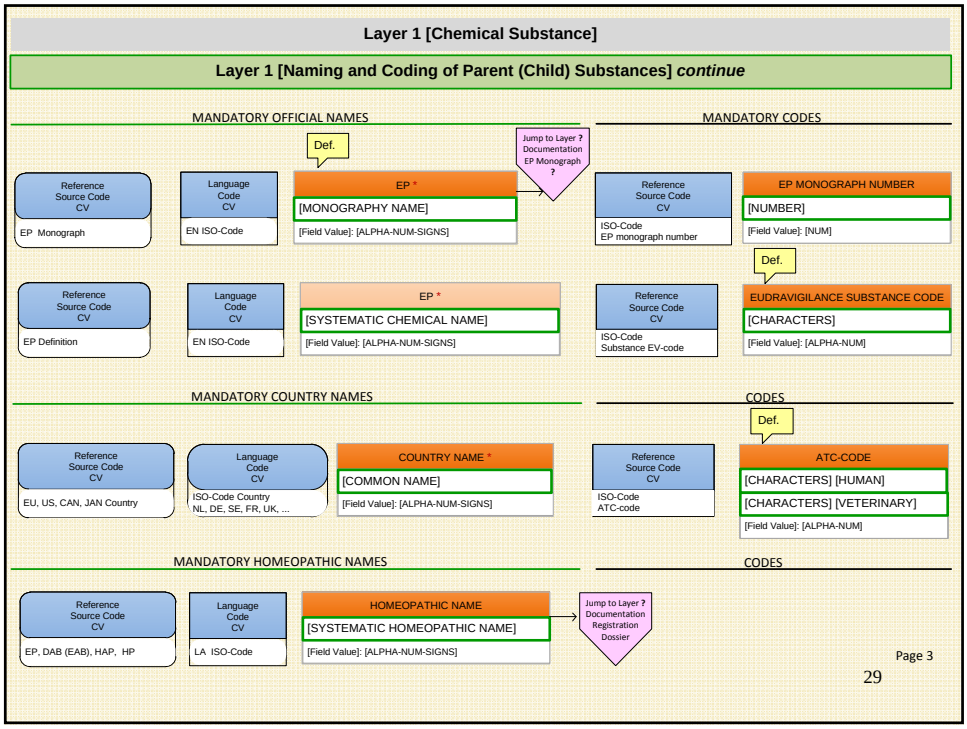
Page 2
28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EN ISO-Code
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EP Definition
Language Code CV
EN ISO-Code
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Substance EV-code
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CODES
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EU, US, CAN, JAN Country
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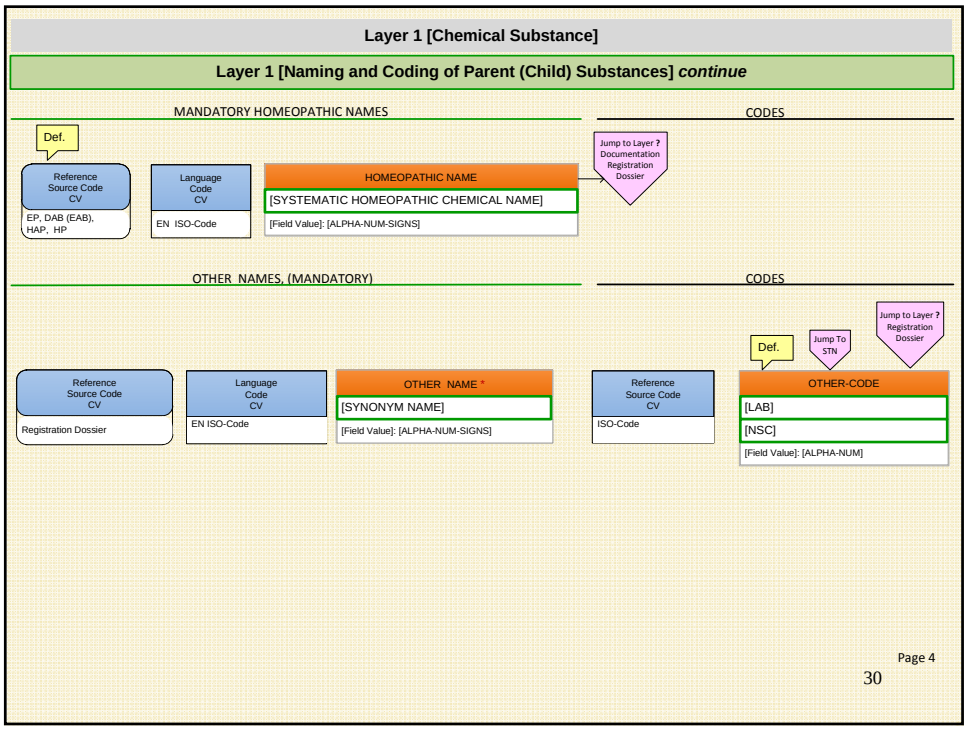
29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Language Code CV
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Page 4
30

PREFERRED NAME:

USP: AMLODIPINE BESYLATE; EP: AMLODIPINE BESILATE;

INN: Amlodipini Besilas [rINNM (la)

INN: Amlodipine Besilate [rINNM (en)]

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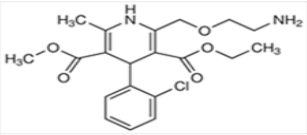
INN: Амлодипина Безилат [rINNM (ru)]



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

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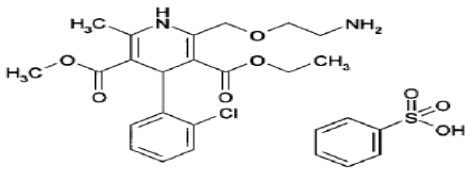
APPLICANT:

- 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**

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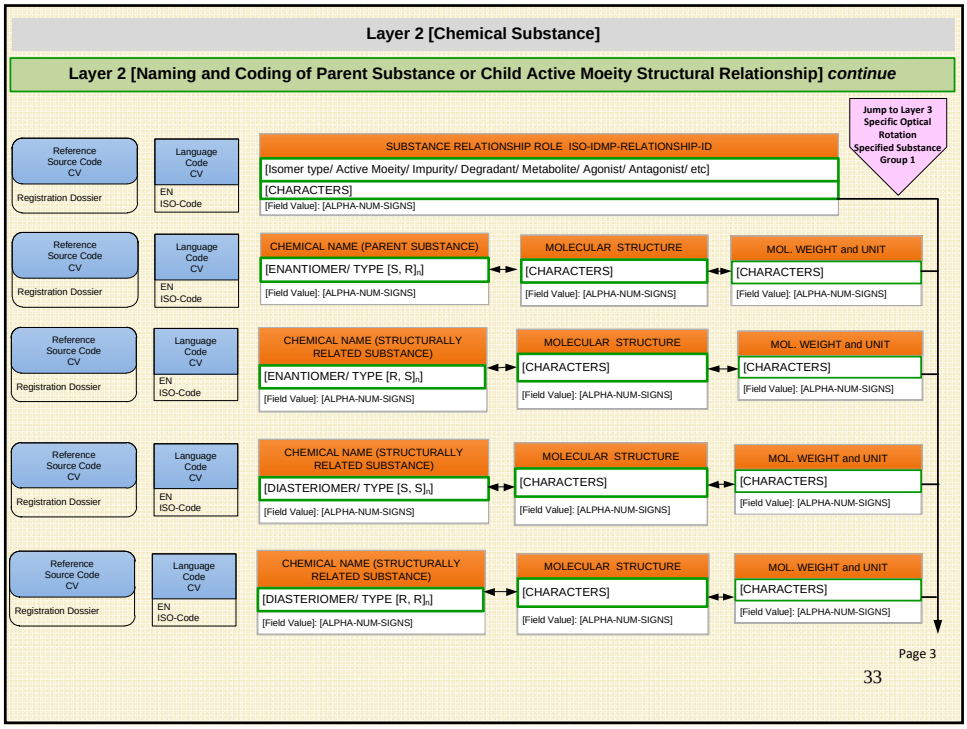

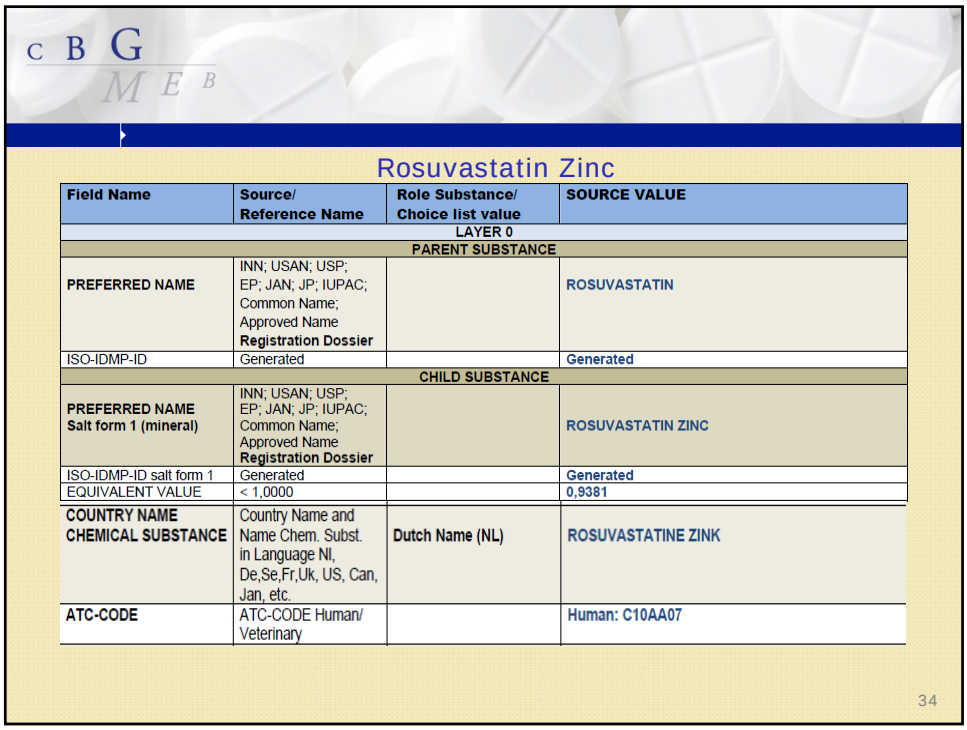

Rosuvastatin Zinc

Field Name	Source/ Reference Name	Role Substance/ Choice list value	SOURCE VALUE
LAYER 0			
PARENT SUBSTANCE			
PREFERRED NAME	INN; USAN; USP; EP; JAN; JP; IUPAC; Common Name; Approved Name **Registration Dossier**		ROSUVASTATIN
ISO-IDMP-ID	Generated		Generated
CHILD SUBSTANCE			
PREFERRED NAME Salt form 1 (mineral)	INN; USAN; USP; EP; JAN; JP; IUPAC; Common Name; Approved Name **Registration Dossier**		ROSUVASTATIN ZINC
ISO-IDMP-ID salt form 1	Generated		Generated
EQUIVALENT VALUE	< 1,0000		0,9381
COUNTRY NAME CHEMICAL SUBSTANCE	Country Name and Name Chem. Subst. in Language Nl, De,Se,Fr,Uk, US, Can, Jan, etc.	**Dutch Name (NL)**	ROSUVASTATINE ZINK
ATC-CODE	ATC-CODE Human/ Veterinary		Human: C10AA07

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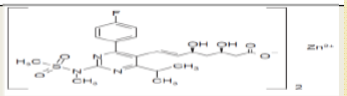
Rosuvastatin Zinc

Field Name	Source/ Reference Name	Role Substance/ Choice list value	SOURCE VALUE
HOMEOPATIC CHEMICAL NAME	Systematic Chemical Homeopathic Name; EP, DAB, HAP, HP		
OTHER NAME REGISTRATION DOSSIER	Synonym Name (s)	7-[4-(4-Fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl] -3,5-dihydroxy-(3R,5S,6E)-6-heptenoic acid zinc salt (2:1); (3R,5S,6E)-7-{4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid zinc salt	
OTHER CODE REGISTRATION DOSSIER	Registration Dossier; Lab-Code; NSC		
LAYER 2			
PARENT/ CHILD SUBSTANCE MANDATORY Mol. Formula; Mol. Weight; Mol. Structure			
MOLECULAR FORMULA	Registration Dossier; STN; EP; USP; Martindale		$(C_{22}H_{27}FN_3O_6S)_2 . Zn$
MOLECULAR WEIGHT	Registration Dossier; EP; USP; Martindale		1026.46 Da [(480.5)$_2$ + 65.38]
INCHI CODE and INCHI KEY	Generated value		
MOLECULAR STRUCTURE	Registration Dossier; EP; USP; Martindale; STN		

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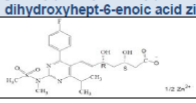
Rosuvastatin Zinc

Field Name	Source/ Reference Name	Role Substance/ Choice list value	SOURCE VALUE
Racemic Mixture [+/-]	Registration Dossier; EP; USP; Martindale	No, Chiral Substance	Two chiral centers [3*R*, 5*S*]
Molecular Structure	Registration Dossier; EP; USP; Martindale		
Molecular Weight	Registration Dossier; EP; USP; Martindale		
Chemical Name (Structurally Related Substance)	Registration Dossier; EP; USP; Martindale	Impurity: Enantiomer type 3S,5R	(3S,5R,6E)-7-{4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid zinc salt
Molecular Structure	Registration Dossier; EP; USP; Martindale		
Molecular Weight	Registration Dossier; EP; USP; Martindale		513.19 Da
Chemical Name (Structurally Related Substance)	Registration Dossier; EP; USP; Martindale	Impurity: RVA-IMP CH_{ac} (Lactone)	N-[4-(4-fluorophenyl)-5-{(E)-2-[(2S,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethenyl}-6-(1-methylethyl)pyrimidin-2-yl]-N-methylmethanesulfonamide
Molecular Structure	Registration Dossier; EP; USP; Martindale		
Molecular Weight	Registration Dossier; EP; USP; Martindale		
Chemical Name (Structurally Related Substance)	Registration Dossier; EP; USP; Martindale	Impurity: RVA-IMP 1 Diasteriomer type [3R,5R]	(3R,5R,6E)-7-{4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid zinc salt

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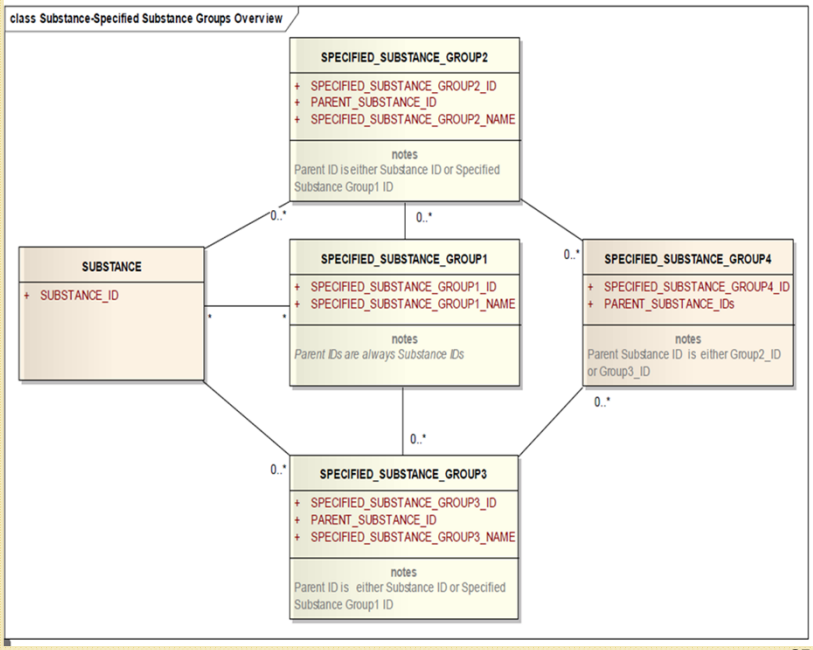

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Documentation Layer

Field Name	Source/ Reference Name	Role Substance/ Choice list value	SOURCE VALUE
LAYER 6			
[PARENT (CHILD) Substances] DOCUMENTATION			
DOMAINS			
PUBLIC DOMAIN			
Scientific Information	Articles/ Textbook		NO
Definitions of Substances/ Monograph	Official Monograph USP/ EP		NO
Data view of Chemical Abstract Register	STNEasy Database, Karlsruhe, Germany		YES
Martindale	Monograph		NO
RESTRICTED DOMAIN; Authorized Persons Competent Authority			
Restricted Domain PART I			
CTD Quality Modules			
Module M2 2.3.S Quality Overall Summary (Substance)	CTD M2		YES
CTD Quality Modules			
Module M3 3.2.S.1: General Properties - Nomenclature - Structure	CTD M3		YES
Module M3 3.2.S.2 Manufacturing - Manufacturer(s) and Sites; - Process and Controls	CTD M3		YES

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Linaclotide, Public domain

WHO: WHO Drug Information, Vol. 21, No. 3, 2007 **Recommended** INN: List 58

linaclotidum
linaclotide [9-L-tyrosine]heat-stable enterotoxin (*Escherichia coli*)-(6-19)-peptide

linaclotide [9-L-tyrosine]entérotoxine thermostable (*Escherichia coli*)-(6-19)-peptide

linaclotida [9-L-tirosina]enterotoxina termoestable (*Escherichia coli*)-(6-19)-péptido

C59 H79 N15 O21 S6

H Cys Cys Glu Tyr Cys Cys Asn Pro
Ala Cys Thr Gly Cys Tyr OH

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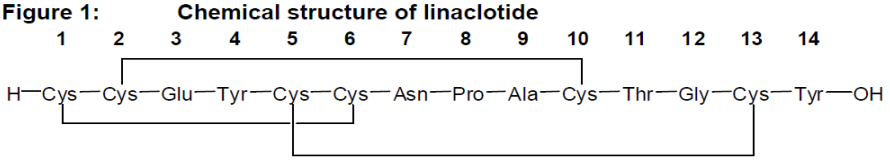
Linaclotide, Restricted Domain

Small Notes ICI:
Mol. Gew,:1.526,8 Da;
Mol. Form.: C59 H79 N15 O21 S6

Linaclotide is a 14-amino acid synthetic peptide with 3 disulfide bonds. All amino acid are of L-configuration. Linaclotide contains three disulfide bridges between Cys^1 and Cys^6, Cys^2 and Cys^{10}, and Cys^5 and Cys^{13}. The chemical structure is shown in the following figure:

Figure 1: Chemical structure of linaclotide



Physically, linaclotide is an amorphous, white to off-white powder, soluble in water and aqueous sodium chloride (0.9%). Sequence length: 14; Sequence: 1 CCEYCCNPAC TGCY; The ES+-data therefore confirms the expected primary sequence of linaclotide: Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (CCEYCCNPACTGCY). Electrospray mass spectrometry shows a monoisotopic mass of 1524.8 Da, in good agreement with the expected value of 1525.4 ± 1 Da for linaclotide.

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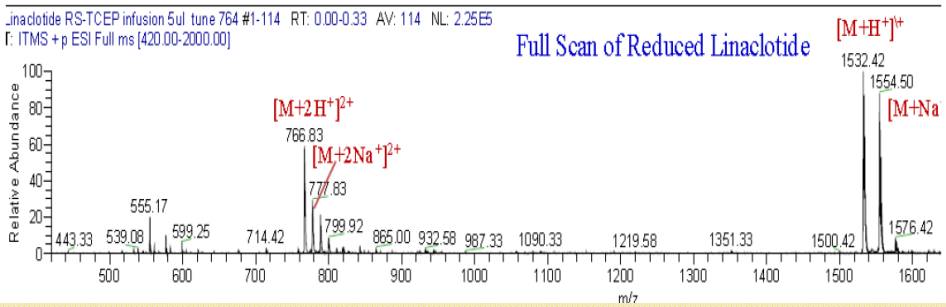
Linaclotide, Restricted Domain

Linaclotide, is a potent and selective guanylate cyclase-C (GC-C) receptor agonist, which is locally acting within the gastrointestinal (GI) tract. This first-in-class, orally administered peptide is structurally related to the guanylin peptide family, which is involved in the regulation of intestinal fluid homeostasis and bowel function. The guanylin family of peptides includes the hormones guanylin and uroguanylin.



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THANK YOU FOR YOUR ATTENTION

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