Change request

Substance

Author	Kristin Gnodtke	Date of request updated	04.02.2022
Project	-	Contact person	-
Dataset release	2022.1	Consulted expert	Roger Mathis

1 Change request input / rationale

The quantity of active ingredients can currently not be represented with the SPHN Dataset Substance and Drug concepts. In addition, there is currently no clear differentiation between manufactured dose form and administrable dose form which are both of type pharmaceutical dose form.

2 Comparison to other standards/data models

2.1 ISO 27269 International Patient Summary (IPS)

The scope is all known medicines taken, or to be taken, by the patient.

Table 16 — Medication Summary Overview (Part1)

Patient clinical data					
Hierarchy: H1	H2	H3	Conformance	Description	Further Details
IPS Section: MEDICATION SUMMARY (PART 1) Synonyms: None Acronyms: None			M	Every PS conformant to IPS SHALL contain this IPS section.	#1
	Medication summary content status		C	Coded Element	#2
	Medications		C	List	#3
		Medication	M	Label Concept	#4

Table 17 — Medication Summary (Part 2)

Patient clinical data							
Hierarchy: H3	H4	H5	H6	H7	Conformance	Description	Further Details
IPS Section: MEDICATION SUMMARY (PART 2 beginning with H3 level) Medication					M	Part 2 comprises a paired list of Medicine and Administration. Labelled Concept	#4
	Reason				O	Label Concept	#5
	Medicinal product				R	Label Concept	#6
		Product code			O	Coded Element	#7
		Product common name (and strength)			RK	String	#8
		Pharmaceutical dose form			R	Coded Element	#9
		Brand name			O	String	#10
		Active ingredients			R	List	#11
			Active ingredient		R	Label Concept	
				Substance code	R	Coded Element	#12
				Strength	R	Ratio	#13
	Administration instruction				R	Label Concept	#14
		Instruction			O	Text	#15
		Period of medication use			R	Period	#16
		Route of administration			O	Coded Element	
		Dose instruction			R	Label Concept	
			No. of units per intake		R	Range or Quantity	#17
			Frequency of intake		R	General Time Specification	#18

Differences to what we currently have in the SPHN Dataset:

- In the SPHN Dataset, we currently have 3 levels of information for being able to express that a medication has been administered or prescribed to a patient; in the IPS, there is information in 7 nested levels (hierarchies) to express the same plus additional information such as medication summary content status (whether there is no information about a medication history or whether there is no medication in the patient's history), strenght of an active ingredient - information we do not currently include
- No distinction between drugs administered and drugs to be taken by the patient
- No. of unit per intake corresponds to substance amount in the SPHN Dataset, e.g. 1 tablet → because the strength per active ingredient is given, the total substance amount can be calculated

2.2 ISO 11616 Pharmaceutical Product Identification

The PhPID (Pharmaceutical Product Identifier) is a unique identifier calculated by an algorithm based on substance identification (ISO 11238), dosage form (ISO 11239) and strengths with units of measurement (ISO 11240). The identifier contains 4 levels:

- Level 1: Substance: Acetaminophen
- Level 2: Substance: Acetaminophen, Strength: 500 mg
- Level 3: Substance: Acetaminophen, Dosage Form: Tablet
- Level 4: Substance: Acetaminophen, Dosage Form: Tablet, Strength: 500 mg.

The major difference between PhPID and GTIN is that PhPID is globally unique and the GTIN is unique within one jurisdiction.

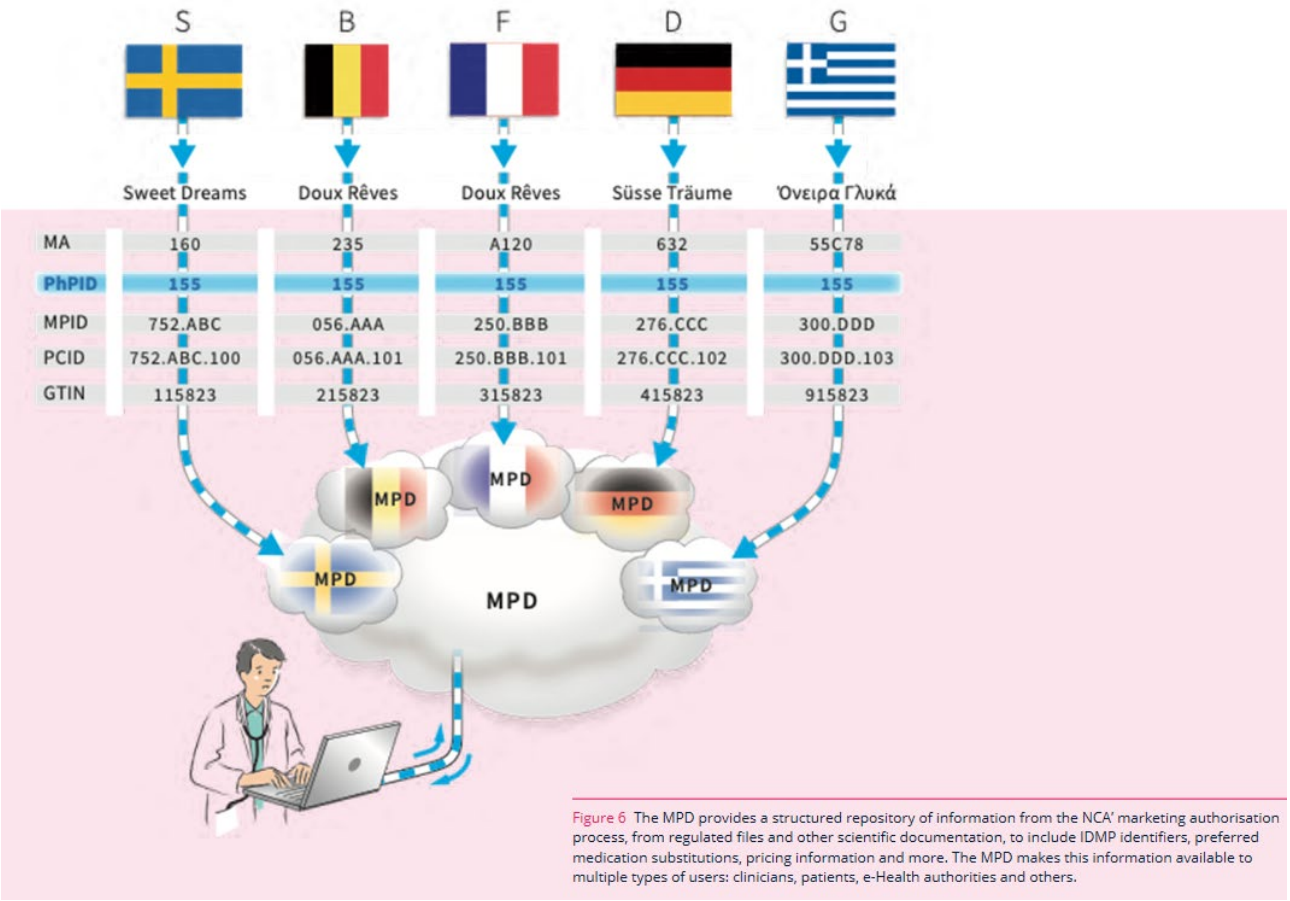

Figure 6 The MPD provides a structured repository of information from the NCA' marketing authorisation process, from regulated files and other scientific documentation, to include IDMP identifiers, preferred medication substitutions, pricing information and more. The MPD makes this information available to multiple types of users: clinicians, patients, e-Health authorities and others.

Source: https://unicom-project.eu/wp-content/uploads/2021/10/UNICOM-handboek_A4_04.pdf

2.3 HL7 FHIR

In HL7 FHIR, there are three resource that correspond to SPHN Dataset concepts related to Medication/Drug:

- Medication → corresponds to Drug in the SPHN Dataset
- Medication Administration → corresponds to Drug Administation Event in the SPHN Dataset
- Medication Dispense → this is the step after prescription and data come from the pharmacy information system, in the SPHN Dataset we have the Drug Prescription concept, but no concept for dispense

In HL7 FHIR, there are as well two different resources (concepts) that hadle actually administered drugs and probably consumed drugs separately.

MedicationDispense	Provision of a supply of a medication with the intention that it is subsequently consumed by a patient (usually in response to a prescription).
MedicationAdministration	When a patient actually consumes a medicine, or it is otherwise administered to them

Name	Flags	Card.	Type	Description & Constraints
Medication	TU		DomainResource	Definition of a Medication Elements defined in Ancestors: id, meta, implicitRules, language, text, contained, extension, modifierExtension
identifier	Σ	0..*	Identifier	Business identifier for this medication
code	Σ	0..1	CodeableConcept	Codes that identify this medication SNOMED CT Medication Codes (Example)
status	?! Σ	0..1	code	active | inactive | entered-in-error Medication status codes (Required)
manufacturer	Σ	0..1	Reference(Organization)	Manufacturer of the item
form		0..1	CodeableConcept	powder | tablets | capsule + SNOMED CT Form Codes (Example)
amount	Σ	0..1	Ratio	Amount of drug in package
ingredient		0..*	BackboneElement	Active or inactive ingredient
item[x]		1..1		The actual ingredient or content
itemCodeableConcept			CodeableConcept	
itemReference			Reference(Substance | Medication)	
isActive		0..1	boolean	Active ingredient indicator
strength		0..1	Ratio	Quantity of ingredient present
batch		0..1	BackboneElement	Details about packaged medications
lotNumber		0..1	string	Identifier assigned to batch
expirationDate		0..1	dateTime	When batch will expire

Differences to what we currently have in the SPHN Dataset:

- We don't capture the manufacturer, not requested by research
- We have the form in Drug Administration Event and in Drug Prescription instead of in Drug
- We have the amount in Drug Administration Event and in Drug Prescription, not in Drug, FHIR has it in all three concepts (amout of drug in package, amount dispensed, dosage-dose = amount of medication per dose)
- If substance is active or inactive, this is represented in FHIR with boolean; in SPHN Dataset we have two separate composedOfs
- We don't capture batch information as not relevant for research

2.4 OMOP CDM

In OMOP, there is the table Drug_exposure. In the vocabularies, there is drug_strength. In the standardized derived elements, there are Drug_era and Dose_era.

Drug exposure: as an example, drug_exposure_start_datetime is defined as "The start date and time for the current instance of Drug utilization. Valid entries include a start date of a prescription, the date a prescription was filled, or the date on which a Drug administration procedure was recorded." (https://www.ohdsi.org/web/wiki/doku.php?id=documentation:cdm:drug_exposure)

Drug strenght: "The DRUG_STRENGTH table contains structured content about the amount or concentration and associated units of a specific ingredient contained within a particular drug product." (https://www.ohdsi.org/web/wiki/doku.php?id=documentation:cdm:drug_strength)

Drug_era: successive periods of Drug Exposures (https://www.ohdsi.org/web/wiki/doku.php?id=documentation:cdm:drug_era)

Dose_era: span of time when the Person is assumed to be exposed to a constant dose of a specific active ingredient (https://www.ohdsi.org/web/wiki/doku.php?id=documentation:cdm:dose_era)

Differences to what we currently have in the SPHN Dataset:

- Drug exposure covers more or less what we have in Drug Administration Event but in OMOP, there is no distinction between drug administration and drug prescription
- in OMOP, there is no general substance table that is reused for drug ingredients, there is only the ingredient_concept_id but amount value is represented per active ingredient

SNOMED CT

In the SNOMED CT Medicinal Product Model Specification v4.0 (2021-06-09), SNOMED International defines Administrative dose form as follows:

Administrable dose form	The (pharmaceutical) dose form of a medicinal product for administration to a patient, after any necessary transformation (from the manufactured dose form) has been carried out

3 Change content

3.1 Currently released concepts

Substance

SPHN Dataset version: 2021.1

Unique concept ID: 0000000363

Concept name	Description	Type	Standard	Value set	Meaning binding SNOMED CT	Meaning binding LOINC
Substance	any matter of defined composition that has discrete existence, whose origin may be biological, mineral or chemical				105590001 |Substance (substance)|	
code	code, name, coding system and version representing the substance, e.g. ATC or SNOMED CT	Code	SNOMED CT, ATC, other	for SNOMED : child of : 105590001 |Substance (substance)|		
generic name	name of the substance, for not yet approved medications the international nonproprietary name (INN) of a substance given by the World Health Organization (WHO)	string				

Drug

SPHN Dataset version: 2021.1

Unique concept ID: 0000000360

Concept name	Description	Type	Standard	Value set	Meaning binding SNOMED CT	Meaning binding LOINC
Drug	medication that can be given to the patient				410942007 |Drug or medicament (substance)|	
product code	code, name, coding system and version representing the drug, e.g. GTIN	Code	GTIN			
active ingredient	pharmaceutically active component of a drug	Substance				
inactive ingredient	inert ingredients or excipients, and generally have no pharmacological effect	Substance				

3.2 Proposed new concept

Substance

Concept name	Description	Type	Standard	Value set	Meaning binding SNOMED CT	Meaning binding LOINC
Substance	any matter of defined composition that has discrete existence, whose origin may be biological, mineral or chemical				105590001 |Substance (substance)|	
code	code, name, coding system and version representing the substance, e.g. ATC or SNOMED CT	Code	SNOMED CT, ATC, other	for SNOMED : child of : 105590001 |Substance (substance)|		
generic name	name of the substance, for not yet approved medications the international nonproprietary name (INN) of a substance given by the World Health Organization (WHO)	string				

substance quantity	quantity of the substance	Quantity			118555000 |Substance amount (property) (qualifier value)|	

Drug

Concept name	Description	Type	Standard	Value set	Meaning binding SNOMED CT	Meaning binding LOINC
Drug	medication that can be given to the patient				410942007 |Drug or medicament (substance)|	
product code	code, name, coding system and version representing the drug, e.g. GTIN	Code	GTIN			
active ingredient	pharmaceutically active component of a drug	Substance				
inactive ingredient	inert ingredients or excipients, and generally have no pharmacological effect	Substance				
manufactured dose form	dose form presented in the manufactured item, e.g. powder and solvent for solution for injection	Code	SNOMED CT	child of : 736542009 |Pharmaceutical dose form (dose form)|	736542009 |Pharmaceutical dose form (dose form)|	74055-5 Dose form of Medication

4 Pros and cons

4.1 Advantages

The amount of substances can be expressed. This can be used in the Drug Administration Event concept for expressing the amount of active ingredients an idividual has been exposed to.

4.2 Disadvantages

None

5 Impact and effort

5.1 Impact on SPHN Dataset

The *Drug Administration Event* Concept and the *Drug Prescription* Concept are affected by the changes.

Currently released concept *Drug Administration Event*

SPHN Dataset version: 2021.1

Unique concept ID: 0000000366

Concept name	Description	Type	Standard	Value set	Meaning binding SNOMED CT	Meaning binding LOINC
Drug Administration Event	single event at which drugs were administered to the patient; this could be a single time point in case of a pill/cream or a duration in case of a single infusion pack or a single patch; one or many drug administration events are initiated by a drug prescription depending on the frequency stated in the prescription				182832007 |Procedure related to management of drug administration (procedure)|	
drug	drug administered to a patient	Drug				
time pattern type	defines if the event is a single time point or a duration (continuous or intermittent)	Time Pattern				
quantity	quantity of a substance administered to an individual at a given time point or over a given time span continuously	Substance Amount				
duration	time interval during which a substance was administered; it is only used for continuously administered substances	Duration				
administration event start time	actual datetime of the start of the administration	temporal				

administration event end time	actual datetime of the end of the administration; the actual end time could be earlier than the calculated end time from start time plus duration; this can occur if the administration is stopped early due to a problem	temporal				
administration route	route of administration of the drug administration event	Code	SNOMED CT	child of : 284009009 |route of administration value (qualifier value)|	284009009 |Route of administration value (qualifier value)|	74050-6 Actual route of administration - attempted or completed [AHRQ]
galenic	galenic of the administered drug, e.g. pill, cream	Code	SNOMED CT	child of : 736542009 |Pharmaceutical dose form (dose form)|	736542009 |Pharmaceutical dose form (dose form)|	74055-5 Dose form of Medication
reason to stop	indication to stop the drug treatment	Code		441308009 |New diagnosis (observable entity)|; 395009001 |Medication stopped - side effect (situation)|; 182872003 |Drug discontinued - too expensive (situation)|; 182846007 |Doctor stopped drugs - medical aim achieved (situation)|; 395007004 |Medication stopped - ineffective (situation)|; 31438003 |Drug resistance (disorder)|; 182845006 |Doctor stopped drugs - avoid interaction (situation)|; 182844005 |Doctor stopped drugs - patient dislikes (situation)|; 419620001 |Death (event)|; 399307001 |Lost to follow-up (finding)|; 74964007 |Other (qualifier value)|		

Proposed new concept *Drug Administration Event*

Concept name	Description	Type	Standard	Value set	Meaning binding SNOMED CT	Meaning binding LOINC
Drug Administration Event	single event at which drugs were administered to the patient; this could be a single time point in case of a pill/cream or a duration in case				182832007 |Procedure related to management of drug administration (procedure)|	

	of a single infusion pack or a single patch; one or many drug administration events are initiated by a drug prescription depending on the frequency stated in the prescription					
drug	drug administered to a patient	Drug				
time pattern type	defines if the event is a single time point or a duration (continuous or intermittent)	Time Pattern				
drug quantity	quantity of a drug administered to an individual at a given time point or over a given time span continuously	Quantity				
duration	time interval during which a substance was administered; it is only used for continuously administered substances	Quantity				
event start datetime	actual datetime of the start of the administration	temporal				
event end datetime	actual datetime of the end of the administration; the actual end time could be earlier than the calculated end time from start time plus duration; this can occur if the administration is stopped early due to a problem	temporal				
administration route	route of administration of the drug administration event	Code	SNOMED CT	child of : 284009009 |route of administration value (qualifier value)|	284009009 |Route of administration value (qualifier value)|	74050-6 Actual route of administration - attempted or completed [AHRQ]
administrable dose form	dose form of the drug for administration to a patient, after any necessary transformation has been carried out, e.g. solution	Code	SNOMED CT	child of : 736542009 |Pharmaceutical dose form (dose form)|	736542009 |Pharmaceutical dose form (dose form)|	74055-5 Dose form of Medication

reason to stop	indication to stop the drug treatment	Code		441308009 |New diagnosis (observable entity)|; 395009001 |Medication stopped - side effect (situation)|; 182872003 |Drug discontinued - too expensive (situation)|; 182846007 |Doctor stopped drugs - medical aim achieved (situation)|; 395007004 |Medication stopped - ineffective (situation)|; 31438003 |Drug resistance (disorder)|; 182845006 |Doctor stopped drugs - avoid interaction (situation)|; 182844005 |Doctor stopped drugs - patient dislikes (situation)|; 419620001 |Death (event)|; 399307001 |Lost to follow-up (finding)|; 74964007 |Other (qualifier value)|		

Currently released concept *Drug Prescription*

SPHN Dataset version: 2021.1

Unique concept ID: 0000000374

Concept name	Description	Type	Standard	Value set	Meaning binding SNOMED CT	Meaning binding LOINC
Drug Prescription	plan that defines at which frequency a drug should be administered to a patient with a given quantity; at every frequency time point a drug administration event should occur				182817000 |Drug prescription (situation)|	
drug	drug prescribed to a patient	Drug				
time pattern type	defines if the event is a single time point or a duration (continuous or intermittent)	Time Pattern				

quantity	quantity of a substance prescribed to an individual	Substance Amount				
frequency	number of drug intakes prescribed per unit of time	Frequency				
first administration datetime	datetime at which the prescribed drug has to be administered for the first time	temporal			413946009 |Date treatment started (observable entity)|	
last administration datetime	datetime at which the prescribed drug has to be administered for the last time	temporal			413947000 |Date treatment stopped (observable entity)|	
administration route	route of administration of the prescription	Code	SNOMED CT	child of : 284009009 |route of administration value (qualifier value)|	284009009 |Route of administration value (qualifier value)|	74050-6 Actual route of administration - attempted or completed [AHRQ]
galenic	galenic of the administered drug, e.g. pill, cream	Code	SNOMED CT	child of : 736542009 |Pharmaceutical dose form (dose form)|	736542009 |Pharmaceutical dose form (dose form)|	74055-5 Dose form of Medication
intent	intention for drug prescription, e.g. palliative care	Intent				
indication to start	indication to start the drug treatment; can be a specific FOPH diagnosis, or a generic reason	qualitative		FOPH diagnosis; neoadjuvant; adjuvant; other; unknown		

Proposed new concept *Drug Prescription*

Concept name	Description	Type	Standard	Value set	Meaning binding SNOMED CT	Meaning binding LOINC
Drug Prescription	plan that defines at which frequency a drug should be administered to a patient with a given quantity; at every frequency				182817000 |Drug prescription (situation)|	

	time point a drug administration event should occur					
drug	drug prescribed to a patient	Drug				
time pattern type	defines if the event is a single time point or a duration (continuous or intermittent)	Time Pattern				
drug quantity	quantity of a drug prescribed to an individual	Quantity				
frequency	number of drug intakes prescribed per unit of time	Quantity				
first administration datetime	datetime at which the prescribed drug has to be administered for the first time	temporal			413946009 |Date treatment started (observable entity)|	
last administration datetime	datetime at which the prescribed drug has to be administered for the last time	temporal			413947000 |Date treatment stopped (observable entity)|	
administration route	route of administration of the prescription	Code	SNOMED CT	child of : 284009009 |route of administration value (qualifier value)|	284009009 |Route of administration value (qualifier value)|	74050-6 Actual route of administration - attempted or completed [AHRQ]
administrable dose form	dose form of the drug for administration to a patient, after any necessary transformation has been carried out, e.g. solution	Code	SNOMED CT	child of : 736542009 |Pharmaceutical dose form (dose form)|	736542009 |Pharmaceutical dose form (dose form)|	74055-5 Dose form of Medication
intent	intention for drug prescription, e.g. palliative care	Intent				
indication to start	indication to start the drug treatment; can be a specific FOPH diagnosis, or a generic reason	qualitative		FOPH diagnosis; neoadjuvant; adjuvant; other; unknown		

6 Discussion

The addition of quantity to the *Substance* concept allows to represent substance amounts for each active ingredient contained in drugs with multiple active ingredients (see chapter 7, example 1). Adding the manufactured dose form to the *Drug* concept allows to provide the galenic form (pharmaceutical dose form) to the researcher even if the administrable dose form data is not present. The manufactured dose form of medications can be retrieved easiely from the hospINDEX database. Distinction between manufactured dose form and administrable dose form allows to represent medications that are provided as solid matter, dissolved in solution for injection and administered to the patient as an injection (see chapter 7, example 2).

7 Examples

Example 1: A patient took 2 tablets of ALGIFOR Dolo Duo Filmtabl 150 mg/500 mg for 3 days in the morning and in the evening from 15.12.2021 – 17.12.2021 during a hospital stay.

Drug – first administration event representing Substance via SNOMED CT

Product code: Identifier: 7680677370014
Name: ALGIFOR Dolo Duo Filmtabl 150 mg/500 mg
Coding system and version: GTIN

Active ingredient: **Substance** : Code : Identifier : 387517004
Name : Paracetamol (substance)
Coding system and version : SNOMED-CT-2021-07-31
Quantity: 1000 mg

Substance : Code : Identifier : 387207008
Name : Ibuprofen (substance)
Coding system and version : SNOMED-CT-2021-07-31
Quantity: 300 mg

Manufactured dose form: 421026006 |Conventional release oral tablet (dose form)|

Drug – first administration event representing Substance via ATC

Product code: Identifier: 7680677370014
Name: ALGIFOR Dolo Duo Filmtabl 150 mg/500 mg

CAVE : ATC code for this product is “N02BE51 paracetamol, combinations excl. psycholeptics”; for expressing quantity for each substance the single substance ATC codes need to be used:

Active ingredient: **Substance** : Code : Identifier : N02BE01
Name : paracetamol
Coding system and version : ATC-2021
Quantity: 1000 mg

Substance : Code : Identifier: M01AE01
Name : ibuprofen
Coding system and version : ATC-2021
Quantity: 300 mg

Manufactured dose form: 421026006 |Conventional release oral tablet (dose form)|

Drug Administration Event
Drug (see above)
Time pattern type: 385432009 |Not applicable (qualifier value)|
Quantity: 2 {pills}
Duration: (empty)
Administration event start time: 15.12.2021
Administration event end time: 15.12.2021
Administration route: 26643006 |Oral route (qualifier value)|
Administrable dose form: 421026006 |Conventional release oral tablet (dose form)|
Reason to stop: (empty)

Example 2: A patient received an injection with FLUIMUCIL 10% Inj Lös 300 mg/3ml on 02.01.2022.

Drug – representing Substance via ATC
Product code: Identifier: 7680668600106
Name: Aspégic Inject Trockensub 0.5 g

Active ingredient: **Substance** : Code : Identifier : N02BA01
Name : acetylsalicylic acid
Coding system and version : ATC-2021
Quantity: 500 mg
Manufactured dose form: 385223009 |Powder for conventional release solution for injection (dose form)|

Drug Administration Event
Drug (see above)
Time pattern type: 385432009 |Not applicable (qualifier value)|
Quantity: 1 {injection}
Duration: (empty)
Administration event start time: 02.01.2022
Administration event end time: 02.01.2022
Administration route: 47625008 |Intravenous route (qualifier value)|
Administrable dose form: 385219001 |Conventional release solution for injection (dose form)|
Reason to stop: (empty)