Section 1. Identification of the substance and the company

1.1 Product identifier

Sacubitril/Valsartan 24/26 mg film-coated tablets
Sacubitril/Valsartan 49/51 mg film-coated tablets
Sacubitril/Valsartan 97/103 mg film-coated tablets

Finished medicinal product intended for the final user.

1.2 Relevant identified uses of the substance, and uses advised against

S+V is a combination of Sacubitril, a neprilisin inhibitor, and Valsartan, an angiotensin II receptor blocker, and is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction, as well as in children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction.

Other uses: NONE.

1.3 Details of SDS supplier

Synthon BV, Microweg 22, 6545 CM, Nijmegen, The Netherlands.
E-mail: info@synthon.com

1.4 Emergency Telephone

+31-(0)24-3727700

Section 2. Hazards identification

2.1 Classification

Exempt from classification and labelling according to Regulation (EC) No 1272/2008 (CLP), as a medicinal product.

2.2 Label elements

***2.2.1* Hazard Pictogram(s)**

Not applicable

2.2.2* *Signal word(s)

Not applicable

2.2.3* *Hazard statement(s)

Not applicable

2.2.4* *Precautionary statement(s)

Not applicable

2.3 Other hazards

See section 9, 11 and 12 for details.

PBT or vPvB properties

This substance/mixture contains no known components considered to be PBT or vPvB at levels of 0.1% or higher, according to REACH (EC) 1907/2006, Annex XIII.

Endocrine Disruptor properties

This substance/mixture contains no known or suspected component identified as having endocrine disrupting properties in accordance with the criteria set out in Article 57f of REACH (EC) 1907/2006, Commission Delegated Regulation (EU) 2017/2100 or Commission Regulation (EU) 2018/605.

Section 3. Composition/information on ingredients

3.1 Substances presenting a health or environmental hazard within the meaning of Regulation (EC) No 1272/2008:

Ingredient Name	*Information on ingredient*	*% (w/w)*	*CLP Classification*
Sacubitril/Valsartan (API)	***CAS number:*** *936623-90-4* ***EC/REACH registration number:*** *810-144-3* ***Chemical Formula:*** $C_{48}H_{55}N_6O_8Na_3 \cdot 2.5H_2O$ ***Assay/Purity:*** *95-100%*	*~27% (for 24/26 mg tab); ~54% (for 49/51 and 97/103 mg tab)*	*Eye Corrosion/Irritation, Cat. 2A; H319* *Skin Sensitizer, Cat. 1B; H317* *Reproductive Toxicity, Cat. 2; H361d*
Other ingredients do not meet the criteria for classification in any hazard class according to Regulation (EC) No. 1272/2008 on classification, labelling and packaging of substances and mixtures.			

Section 4. First aid measures

4.1. Description of first aid measures

4.1.1. Inhalation

If symptoms are experienced, remove source of contamination or move victim to fresh air. Obtain medical advice (show this SDS).

4.1.2. Skin

Remove contaminated clothing, shoes and leather goods (e.g. watchbands, belts). Flush with lukewarm, gently flowing water for 5 minutes. If irritation persists, repeat flushing. Obtain medical advice (show this SDS).

4.1.3. Eyes

Quickly and gently, blot or brush residue off the face. Immediately flush the contaminated eye(s) with lukewarm, gently flowing water for 15-20 minutes, while holding the eyelid(s) open. If a contact lens is present, DO NOT delay irrigation or attempt to remove the lens. Take care not to rinse contaminated water into the unaffected eye or onto the face. Immediately obtain medical attention. (show this SDS).

4.1.4. Ingestion

If irritation or discomfort occur, obtain medical advice (show this SDS).

4.2. Most important symptoms and effects, both acute and delayed

4.2.1 Acute

5 Hypotension is the most likely symptom of overdose.
Consider effects related to the classification of the compound (see section 11).

5.2.1 Delayed

The most common adverse effects are hypotension, hyperkalemia, cough, dizziness, and renal failure. And may cause angioedema. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Oligohydramnios has also been reported.
Consider effects related to the classification of the compound (see section 11).

4.3 Indication of any immediate medical attention and special treatment needed

Provide general supportive measures and treat symptomatically.
If medical advice is required, contact a physician and show this SDS.
General measures should be taken to eliminate the substance and to reduce absorption.

Section 5. Fire-fighting measures

5.1 Extinguishing media

5.1.1 Appropriate extinguishing media

Use water, dry chemical powder (ABC) or appropriate foam.

5.1.2 Unsuitable/inappropriate extinguishing media

No information available.

5.2 Special hazards arising from the substance or mixture

No information available.

5.3 Advice for firefighters

Avoid exposure to the compound. Fire fighters should use self-containing breathing apparatus and protective chemical-resistant clothing to prevent contact with skin and eyes.

Section 6. Accidental release measures

6.1. Personal precautions, protective equipment and emergency procedures

6.1.1. For non-emergency personnel

Avoid breathing hazardous vapors/dusts. Take immediate action if necessary and considered safe. Respiratory protection should be effective against residual fine dust. Use an (FF)P3 filter (USA: N100 or P100). Wear suitable protective clothing (e.g. made from Tyvek material) and safety goggles. Wear nitrile chemical-mechanical-resistant gloves, check solvent compatibility of gloves where relevant. For major spills, involvement of the fire brigade or other local authorities should be considered.

6.1.2 For emergency responders

See row above and/or section 8.

6.2. Environmental precautions

Keep away from drains, surface- and groundwater, and soil.
Do not release into the environment.
Prevent further leakage or spillage if safe to do so.
Local authorities should be advised if significant spillages cannot be contained.

6.3. Methods and material for containment and cleaning up

Wear protective clothing. See section 6.1

6.3.1. Containment of spill

Provide a cover or protection to prevent damage or spillage.
Do not sweep. Wet clean or vacuum up solids.
Clear spills immediately.

6.3.2. Clean-up

Clean the spill with universal sorbent sheets, towels/tissues, a HEPA-filtered vacuum cleaner etc. Work from the surrounding area towards the location of the actual spill. Dispose the spill into containers labelled as hazardous material if required. Repeat cleaning if required with mopping or wet wiping.

6.3.3. Other information

Wastes must be properly contained and labelled for disposal.
When clearing up spilt material avoid breathing dust, and skin contact. Before clear up dampen solid waste or preferably use a permitted industrial vacuum cleaner.

6.4. Reference to other sections

Refer to section 8, 11, 12 and 13 for additional information.

Section 7. Handling and storage

7.1 Precautions for safe handling

Work in an area with general and local ventilation, if possible in a contained area. Prevent aerosol and dust generation. Keep container closed when not in use.
Do not eat, drink or smoke when using this product.
Contaminated work clothing should not be allowed out of the workplace.

Sacubitril/Valsartan API
P202: Do not handle until all safety precautions have been read and understood.
P261: Avoid breathing dust/fume/gas/mist/vapours/ spray.
P280: Wear protective gloves/protective clothing/eye protection/face protection.
P308 + P313: IF exposed or concerned: Get medical advice/attention.
P302/305+351: IF IN EYES/ON SKIN: Rinse cautiously with water for several minutes.
P264+P265: Wash hands thoroughly after handling. Do not touch eyes.

7.1.1 Protective measures

Measures to prevent fire: This material is assumed to be combustible. It is advisable to dissipate the potential build-up of static electricity by grounding mechanical equipment in contact with the dry material (as with all dry powders).
Measures to prevent aerosol/dust generation: See section 8.2.
Measures to protect the environment: Keep away from drains, surface- and groundwater, and soil.

7.1.2 Advice on general occupational hygiene

Wear protective clothing (e.g. lab coat) and safety glasses, apply hygienic working habits (e.g. no drinking, eating or smoking at the workplace).

7.2 Conditions for safe storage, including any incompatibilities

Store locked up in a dry and cool place. Also, see supplementary information, e.g. shipping documentation, CoA or contact Synthon. Select storage locations and packaging material in line with relevant local chemical storage guidelines where relevant.

7.3 Specific end use(s)

Sacubitril/Valsartan tablets are finished medicinal products indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction, as well as in children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction.

Section 8. Exposure controls/personal protection

8.1. Control parameters

8.1.1. National limit values

CAS No.	*Name*	*National limit values*
936623-90-4	Sacubitril/Valsartan (API)	No OELs set by competent authorities available that correspond to union occupational exposure limit values in accordance with directive 98/24/EC and article 2(3) of 2014/113/EU.
No other relevant substances present in product.		

8.1.2. Currently recommended monitoring procedures

Please refer to local legislation. Alternatively, reference to the ISPE good practice guide, ISBN 978-1-936379-35-4 is advised.

8.1.3. Exposure limit values

The drug product does not have an exposure limit.

CAS No.	*Name*	*OEL value (unit)*
936623-90-4	Sacubitril/Valsartan (API)	60 µg/m^3 (8 hr. TWA) by Originator
No other relevant substances present in product.		

8.1.4. DNELs and PNECs

Synthon DNEL = -

PNEC= -

8.1.5. Control Banding

Synthon OEB: not assigned for finished products/mixtures.

8.2. Exposure controls

Ingredients (tablet residual powder) can possibly enter the body through inhalation, ingestion and via the skin.

8.2.1 Appropriate engineering controls

Intact tablets are not considered hazardous under normal handling procedures and special protective equipment - other than those mentioned below - is not required.

Open handling: if residual dust is present in bulk packaging use an (FF) P3 filter (USA: N100 or P100).

8.2.2. Individual protection measures, such as personal protective equipment

Eye and face protection

Safety glasses recommended.

Skin protection

Hand protection: Wear gloves, for dust any glove is suitable, check liquid compound or solvent compatibility of gloves where relevant.

Other skin protection: Wear suitable protective clothing (e.g. lab coat).

Respiratory protection:

If required: Use a (FF)P3 filter (USA: N100 or P100).

Thermal hazards

Not applicable

8.3. Environmental exposure controls

Keep away from drains, surface- and groundwater, and soil.

Moisten spilled product with water and collect in containers for disposal. Rinse remnant with plenty of water.

Section 9. Physical and chemical properties

9.1. Basic physical and chemical properties

Appearance (Sacubitril/Valsartan 24/26 mg tablets)	*White oval biconvex film-coated tablet debossed with "S7V" on one side and "L1" on the other side*
Appearance (Sacubitril/Valsartan 49/51 mg tablets)	*Pink oval biconvex film-coated tablet debossed with "S7V" on one side and "M2" on the other side*

Appearance (Sacubitril/Valsartan 97/103 mg tablets)	*Pink oval biconvex film-coated tablet debossed with "S7V" on one side and "H3" on the other side*
Odor	*Not applicable*
Melting point/freezing point	*Not applicable*
Boiling point or initial boiling point and boiling range	*Not applicable*
Flammability	*Not applicable*
Lower and upper explosion limit	*Not applicable*
Flash point	*Not applicable*
Auto-ignition temperature	*Not applicable*
Decomposition temperature	*Not applicable*
pH	*Not applicable*
Kinematic viscosity	*Not applicable*
Solubility	*Not applicable*
(log) Partition coefficient n-octanol/water	*Not applicable*
Vapor pressure	*Not applicable*
Density and/or relative density	*Not applicable*
Relative vapor density	*Not applicable*
Particle characteristics	*Not applicable*

9.2. ***Other information***

9.2.1. ***Physical hazards***

No data (publicly) available or generated.

9.2.2. ***Other safety characteristics***

No data (publicly) available or generated.

Section 10. Stability and Reactivity

10.1. **Reactivity**

Not considered a reactive compound.

10.2. **Chemical stability**

Store under the storage conditions given in section 7 of this SDS.

10.3. **Possibility of hazardous reactions**

No hazardous reactions are expected to occur.

10.4. **Conditions to avoid**

For general advice see section 7.

10.5. **Incompatible materials**

Not known.

10.6. **Hazardous decomposition products**

Not known. See section 5.

Section 11. Toxicological information on drug substance (Sacubitril/Valsartan)

Other ingredients of the drug product (mixture) do not meet the criteria for classification in any hazard to health classes according to Regulation (EC) No. 1272/2008 on classification, labelling and packaging of substances and mixtures.

11.1 Toxicological effect (Sacubitril+Valsartan API)

11.1.1 Acute toxicity

Inhalation

No data (publicly) available or generated.

Oral

NOEL: mouse, 2000 mg/kg

NOEL: rat, 2000 mg/kg

Dermal

No data (publicly) available or generated.

11.1.2 Skin corrosion/irritation

Based on available data, the classification criteria are not met.

No skin irritation observed in rabbits (OECD 404)

11.1.3 Serious eye damage/irritation

Eye irritation observed in rabbits (OECD 405)

11.1.4 Respiratory sensitization

No data (publicly) available or generated.

11.1.5 Skin sensitization

Weakly sensitizing in mouse (4/8 mice, OECD 429)

Weakly sensitizing in guinea pig (OECD 406)

11.1.6 Germ cell mutagenicity

Based on available data the classification criteria are not met.

Ames-Test: Negative

In vitro Chromosome Aberration Study: Negative (peripheral human lymphocytes)

In vivo Micronucleus Test: Negative (rat bone marrow cells)

11.1.7 Carcinogenicity

Based on available data the classification criteria are not met.

Carcinogenicity studies conducted in mice and rats with Sacubitril and Valsartan did not identify any carcinogenic potential up to 19 and 4 times the recommended human dose, respectively.

Not listed by IARC, NTP or OSHA.

11.1.8 Reproductive toxicity

Suspected human reprotoxicant. Exposure during organogenesis, gestation and lactation may affect pup development and survival. Adverse embryo-foetal effects attributed to angiotensin receptor antagonist activity. Sacubitril and its active metabolite LBQ657 are excreted in human milk in very low amounts (≤ 0.01%).

NOAEL: 3 mg/kg (rabbit, oral) Embryo-Fetal Development, Teratogenicity at maternally toxic dose;
NOAEL: 200 mg/kg/day (rat, oral) Embryo-Fetal Development, Maternal toxicity;
NOAEL: 50 mg/kg (rat, oral) Fertility and early Embryonic Development, Paternal toxicity;
NOEL: 150 mg/kg/day (rat, oral) Fertility and early Embryonic Development, NO FERTILITY EFFECTS;
NOAEL: 30 mg/kg (rat, oral) Embryo-Fetal Development, Fetotoxicity at maternally non toxic dose

11.1.9 STOT-single exposure

Based on available data, the classification criteria are not met.

11.1.10 STOT-repeated exposure

Based on available data, the classification criteria are not met.
NOAEL (Multiple organs): 30 mg/kg/day (rat, oral, 26-week duration; dosed at ≤ 100 mg/kg;)
NOAEL (Kidneys): 30 mg/kg/day (monkey, oral, 39-week duration; dosed at ≤ 300 mg/kg)
Gastrointestinal tract (mouse, oral, 13-week duration; dosed at ≤ 400 mg/kg)

11.1.11 Aspiration hazard

No data (publicly) available or generated.

11.2 Other hazards

11.2.1 Endocrine disrupting properties

Not a human endocrine disruptor.

11.2.2 Other information

Pharmacokinetics

The valsartan contained within sacubitril/valsartan is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in sacubitril/valsartan is equivalent to 40 mg, 80 mg and 160 mg of valsartan in other marketed tablet formulations, respectively. Sacubitril/valsartan dissociates into valsartan and the prodrug sacubitril, which is further metabolized to the active metabolite LBQ657. These reach peak plasma concentrations in 2 hours, 1 hour, and 2 hours, respectively. Oral bioavailability of sacubitril and valsartan is > 60% and > 23%, respectively. Following twice daily dosing of sacubitril/valsartan, steady-state levels of sacubitril, LBQ657 and valsartan are reached in three days. Sacubitril, LBQ657 and valsartan are highly bound to plasma proteins (94-97%). Average apparent volume of distribution of valsartan and sacubitril are 75 to 103 L, respectively. Valsartan is minimally metabolized, with ~20% of dose recovered as metabolites. CYP450-enzyme-mediated metabolism of sacubitril and valsartan is minimal. Following oral administration, 52-68% of sacubitril (primarily as LBQ657) and ~13% of valsartan and its metabolites are excreted in urine; 37-48% of sacubitril (primarily as LBQ657) and 86% of valsartan and its metabolites are excreted in feces. Sacubitril, LBQ657 and valsartan have elimination half-lives of ~1.43 hours, 11.48 hours, and 9.90 hours, respectively.

Other Toxicity Tests:

Phototoxicity: No data (publicly) available or generated.
Clinical: Most commonly reported adverse reactions in adults during treatment with sacubitril/valsartan were hypotension (17.6%), hyperkalaemia (11.6%) and renal impairment (10.1%). Angioedema was also reported in patients (0.5%). Other commonly reported adverse reactions included headache, dizziness, syncope, vertigo, diarrhea, nausea, cough, gastritis and fatigue.

Section 12. Ecological information on Drug Substance (Sacubitril/Valsartan API)

Other ingredients of the drug product (mixture) do not meet the criteria for classification in any hazard to the aquatic environment classes according to Regulation (EC) No. 1272/2008 on classification, labelling and packaging of substances and mixtures.

12.1 Toxicity

12.1.1 96 hr LC_{50} (for fish)

No data (publicly) available or generated.

12.1.2 ***48 hr EC_{50} (for crustacea)***
EC_{50} >100 mg/L; NOEC: 100 mg/L (*Daphnia magna*, 48 h)
Method: 92/69/EEC (L383) C.2

12.1.3 ***72 or 96 hr ErC_{50} (for algae or other aquatic plants)***
ErC_{50} >100 mg/L; EbC_{50} >100 mg/L; NOEC: 100 mg/L
(*Pseudokirchneriella subcapitata*, 72 h)
Method: 92/69/EC (L383) C.3

12.1.4 ***Inhibitory effects micro-organism***
EC_{20} >300 mg/L; EC_{50} >300 mg/L; EC_{80} >300 mg/L (activated sludge, 3 h)
Method: OECD 209

12.1.5 ***Chronic NOEC or ECx (for fish)***
No data (publicly) available or generated.

12.1.6 ***Chronic NOEC or ECx (for crustacea)***
No data (publicly) available or generated.

12.1.7 ***Chronic NOEC or ECx (for algae or other aquatic plants)***
No data (publicly) available or generated.

12.1.8 ***Other***
PNEC Exposure Control Value: 560 µg/L

12.2 **Persistence and degradability**
Not readily degradable.
(28 days at 23.4 °C; Degradation: 0 %; Initial Concentration: 20 mg DOC/L)
Method(s): 92/69/EC (L383) C.4-B (Modified OECD screening test)

12.3 **Bioaccumulative potential**

12.3.1 ***(log) Partition coefficient n-octanol/water***
Exposure Control Value: 560 µg/L

12.3.2 ***Bioconcentration factor***
No data (publicly) available or generated.

12.4 **Mobility in soil**
No data (publicly) available or generated.

12.5 **Results of PBT and vPvB assessment**
Compound not considered as PBT or vPvB.

12.6 **Endocrine disrupting properties**
No data (publicly) available or generated.

12.7 **Other adverse effects**
No data (publicly) available or generated.

Section 13. Disposal considerations

13.1. **Waste treatment methods**
Handle as chemical waste. Dispose according to Federal-, State- or Local laws. Keep away from drains, surface- and ground-water, and soil. Please contact a EHS representative for additional information.

Handling of waste complies with Directive 2008/98/EC
Waste management is carried out without endangering human health, without harming the environment and, in particular: (a) without risk to water, air, soil, plants or animals; (b) without causing a nuisance through noise or odors; and (c) without adversely affecting the countryside or places of special interest.

Chronological record of the quantity, nature and origin of the waste, and, where relevant, the destination, frequency of collection, mode of transport and treatment method foreseen in respect of the waste, is available, on request, to the competent authorities.

Section 14. Transport information

14.1. UN number
Not relevant/required.

14.2. UN proper shipping name
Sacubitril/Valsartan

14.3. Transport hazard classes
ADR/RID: Not subject to ADR/RID.
ICAO/IATA: Not subject to ICAO/IATA.
TARIC: 3004 90 00 00

14.4. Packing Group
Not relevant/required.

14.5. Environmental hazards
Not environmentally hazardous. See section 12.

14.6. Special precautions for user
None known.

14.7. Maritime transport in bulk according to IMO instruments
Not relevant.

14.8. Other information
Pharmaceutical products (medicines), ready for use, which are substances manufactured and packaged for retail sale or distribution for personal or household consumption, are exempted from the requirements of ADR.

Section 15. Regulatory information

15.1. NOTABLE and/or APPLICABLE safety, health and environmental regulations/legislation for the substance:
Regulation (EC) No 1005/2009, 16 September 2009 on substances that deplete the ozone layer: *NOT APPLICABLE*
Directive 2012/18/EU (Seveso-III), 24 July 2012: *NOT APPLICABLE*
Regulation (EC) No 1907/2006, 14 October 2022: Restrictions on the manufacture, placing on the market and use of certain dangerous substances, preparations and articles (Annex XVII)**:** *NOT APPLICABLE*
Regulation (EC) 1907/2006, 14 October 2022: Candidate List of Substances of Very High Concern for Authorization (Article 59): *NOT APPLICABLE*
Regulation (EC) 1907/2006, 14 October 2022: List of substances subject to authorization (Annex XIV): *NOT APPLICABLE*
Regulation (EC) No 850/2004, 29 April 2004: *Persistent organic pollutants: NOT APPLICABLE*

15.2. Chemical safety assessment (as part of EU-REACH, (EC) No 1907/2006).
To our knowledge, no CSA is required for this compound.

Section 16. Other information

16.1. Revisions

New template being used, which complies with (EC) No 1907/2006 (REACH), Globally Harmonized System (GHS), and Regulation (EC) No 1272/2008 (CLP).

16.2. Abbreviations

CLP: Classification, Labelling & Packaging
OEB: Occupational Exposure Band
OEL: Occupational Exposure limit
STOT: Specific Target Organ Toxicity
IARC: International Agency for Research on Cancer
NTP: National Toxicology Program (USA)
OSHA: Occupational Safety and Health Administration

16.3. Key data sources

European Medicines Agency. Summary of Product Characteristics. Entresto. 2026.
(Originator) ENTRESTO® SPRINKLE 6mg/6mg, 15mg/16mg ORAL PELLETS. Safety Data Sheet. Novartis Pharma AG. Issued: 8-7-2024.
(Originator) ENTRESTO® Tablet. Safety Data Sheet. Novartis Pharma AG. Issued: 9-30-2021.
SDS.NL01.51543(2.0)

16.4. Training advice

Distribute this SDS and relevant additional information to appropriate employees. If necessary, provide sufficient training to personnel with regard to safe working with hazardous materials.