SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nutratain powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial with 932 mg dry substance (powder) contains:

1.	Retinol (Vitamin A)	0.99	mg	equivalent to Retinol (Vitamin A)	3300 IU
	(as retinol palmitate)	1.82	mg		
2.	Cholecalciferol	0.005	mg	equivalent to Vitamin D_3	200 IU
3.	all-rac-α-tocopherol (Vitamin E)	9.11	mg		
4.	all-rac-Phytomenadione (Vitamin K_1)	0.15	mg		
5.	Ascorbic acid (Vitamin C)	200	mg		
6.	Thiamine (Vitamin B_1)	6.00	mg		
	(as Thiamine hydrochloride)	7.63	mg		
7.	Riboflavin (Vitamin B_2)	3.60	mg		
	(as Riboflavin sodium phosphate hydrate)	4.58	mg		
8.	Pyridoxine (Vitamin B_6)	6.00	mg		
	(as Pyridoxine hydrochloride)	7.30	mg		
9.	Cyanocobalamin (Vitamin B_{12})	0.005	mg		
10.	Folic acid (Vitamin B_9)	0.60	mg		
	(as Folic acid hydrate)				
11.	Pantothenic acid (Vitamin B_5)	15.0	mg		
	(as Dexpanthenol)	14.0	mg		
12.	Biotin (Vitamin B_7)	0.06	mg		
13.	Nicotinamide (Vitamin B_3)	40.0	mg		

Excipient(s) with known effect: This medicinal product contains up to 2 mmol (46 mg) sodium per vial, see section 4.4.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion
Yellow-orange cake or powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Parenteral vitamin substitution, when oral or enteral nutrition is impossible, insufficient or contraindicated.
Nutratain is indicated in adults and children aged 11 years and older.

4.2 Posology and method of administration

Posology

Adults, adolescents and children aged 11 years and older:
1 vial per day

Elderly
The adult dose does not necessarily have to be adjusted because of age per se. However, the physician should be aware of the increased risk of conditions that can affect the dosage in this population (see section 4.4).

Patients with hepatic and renal impairment:
Plasma levels of the vitamins should be monitored during administration and the dosage should be adjusted accordingly.

Paediatric population-Children aged under 11 years of age:
Nutratain is contraindicated in newborns, infants and children under 11 years of age.

Note:
When administering Nutratain together with other vitamin containing products, the total amount of these vitamins have to be taken into account to avoid overdose.

Method of administration
Intravenous use.
Nutratain should be administered slowly. Administration time and infusion rate depend on the recommendations of the infusion solution (see section 6.6).

Precaution to be taken before manipulating or administering the product
Nutratain must only be used as additive to infusion solutions. After reconstitution in water for injection or NaCl 0.9% w/v or glucose 5% w/v, it is diluted in compatible solutions/emulsions for infusion (see section 6.6). Only use if the reconstituted solution is clear and yellow-orange in colour.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, including soy protein/soy products or peanut protein/peanut products.
- Newborns, infants and children under 11 years of age
- Pre-existing hypervitaminosis
- Severe hypercalcaemia, hypercalciuria or any treatment, disease and/or disorder that can result in severe hypercalcaemia and/or hypercalciuria (e.g. tumours, skeletal metastases, primary hyperparathyroidism, granulomatosis, etc.).
- Combination with vitamin A or retinoids (see section 4.5).

4.4 Special warnings and precautions for use

Warnings

Mild to severe systemic hypersensitivity reactions have been reported for the ingredients of Nutratain (including vitamin B_1, B_2, B_{12}, folic acid, soy lecithin and cross-allergic reactions to soybean and peanut protein), see section 4.8. The infusion or injection must be stopped immediately if signs or symptoms of a hypersensitivity reaction develop.

One vial per day is intended to cover the normal daily vitamin requirements and maintenance of vitamin homeostasis. If there are specific deficiencies of individual vitamins, individual supplementation of these vitamins is required. Additional vitamins from other sourcesneed to be taken into account to avoid overdose and toxic effects.

The risk for hypervitaminosis A and vitamin A toxicity is increased in, e.g. patients with protein malnutrition, with renal impairment (even in the absence of vitamin A supplementation), with hepatic impairment, paediatric patients and patients on long-term treatment. Acute hepatic disease in patients with saturated hepatic vitamin A stores can lead to the manifestation of vitamin A toxicity.

Alcohol promotes hepatic vitamin A depletion and enhances vitamin A toxicity. Therefore special care needs to be taken on patients with chronic alcohol abuse.

Excessive quantities of vitamin D can cause hypercalcaemia and hypercalciuria. The risk of vitamin D toxicity is greater in patients with diseases and/or disorders that can cause hypercalcaemia and/or hypercalciuria and patients on chronic vitamin therapy.

Although extremely rare, excessive quantities of vitamin E can impair wound healing because of platelet dysfunction and disorders of blood coagulation. The risk of vitamin E toxicity is greater in patients with impaired hepatic function, patients with coagulation disorders or on oral anticoagulation therapy and patients on chronic vitamin therapy.

Folic acid and vitamin K may lead to gastrointestinal disorders, when large doses are applied.

Special precautions for use

<u>Monitoring</u>

Total vitamin intake from all sources, such as nutritional sources (e.g. fat emulsions), other vitamin supplementation or medicinal products possibly interacting with Nutratain (see section 4.5), should be noted.

Clinical status and vitamin plasma levels (especially vitamins A, D and E) should be monitored regularly, especially in patients with hepatic dysfunction, renal insufficiency and patients which require long-term administration.

Patients receiving parenteral multivitamins as the only vitamin source over long periods of time should be monitored to ensure adequate supplementation.

Rapid refeeding of malnourished or depleted patients may cause refeeding syndrome characterised by severe electrolyte and fluid shifts associated with metabolic complications. Refeeding requires minerals such as phosphate and magnesium and cofactors such as thiamine. Therefore vitamin

supplementation should also be started with refeeding. An adequate supply of thiamine should be provided.

Due to the content of Vitamin K, the coagulation factors of the patient should be monitored regularly.

An increase in bile acid levels (total and individual bile acids including glycocholic acid) has been reported in patients receiving multivitamin supplementation. Because of the content of glycocholic acid in Nutratain, close monitoring of liver function is recommended.

Some vitamins (especially A, B_2 and B_6), are sensitive to ultraviolet light (e.g. direct or indirect sunlight). In addition, loss of, particularely vitamin A, B_1, C and D can result from higher oxygen levels in the solution. These factors should be considered if sufficient vitamin levels are not achieved.

General monitoring of parenteral nutrition

Hepatobiliary disorders including cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure, as well as cholecystitis and cholelithiasis, are known to develop in some patients on parenteral nutrition (including vitamin-supplemented parenteral nutrition). Therefore, monitoring of liver function parameters is recommended in patient on parenteral nutrition receiving Nutratain. Patients developing abnormal laboratory parameters or other signs of hepatobiliary disorders should be assessed early by a clinician knowledgeable in liver diseases in order to identify possible causative and contributory factors and possible therapeutic and prophylactic interventions.

Patients with hepatic impairment

Patients with impaired liver function may need individualised vitamin supplementation. Special attention needs to be payed to the vitamin A levels, because the presence of liver disease is associated with increased susceptibility to vitamin A toxicity, especially in patients with chronic alcohol abuse. Because of the content of glycocholic acid, careful monitoring of the liver function is mandatory in the case of repeated or long-term administration of Nutratain.

Patients with renal impairment

Patients with renal impairment have a potential risk of overdose/toxicity in the pre-dialysis phase due to the decreased ability of renal excretion of excess water-soluble vitamins. While on dialysis, the loss of vitamins, especially water-soluble vitamins, may lead to increased vitamin requirements Individualized vitamin supplementation may be needed, depending on the degree of renal impairment and the presence of comorbidities. Special attention needs to be payed to patients with severe renal insufficiency to maintain vitamin D status and to prevent vitamin A toxicity.

Use in patients with vitamin B_{12} deficiency

In patients at risk for vitamin B_{12} (cyanocobalamin) deficiency, e.g. patients with short bowel syndrom, inflammatory bowel disease, use of metformin > four months, use of proton pump inhibitors or histamine H_2 blockers > 12 months, vegans or strict vegetarians, and adults older than 75 years, and/or when treatment over several weeks is planned, evaluation of vitamin B_{12} status is recommended before starting treatment with Nutratain.

After several days of administration, the individual amounts of both cyanocobalamin (vitamin B_{12}) and folic acid in Nutratain may be sufficient to result in an increase in red blood cell count, reticulocyte count and haemoglobin values in some patients with vitamin B_{12} deficiency-associated megaloblastic anaemia. This may be masking an existing vitamin B_{12} deficiency, which requires higher doses of cyanocobalamin than provided in Nutratain.

When interpreting levels of vitamin B_{12}, it should be taken into account that recent intake of vitamin B_{12} may result in normal levels despite a tissue deficiency.

Paediatric patients
Nutratain is contraindicated in newborns, infants and children under 11 years of age.

Elderly patients
In general, dosage adjustments (reducing the dose and/or extending the dosing intervals) for elderly patients should be considered due to their advanced age and the accompanied greater frequency of decreased hepatic, renal or cardiac function and also due to concomitant diseases or medication.

Special warnings/precautions regarding excipients
This medicinal product contains up to 2 mmol (46 mg) sodium per vial, equivalent to 2.3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interference with serological testing
The product should not be administered prior to blood sampling for the detection of megaloblastic anaemia (pernicious anemia), because administered folic acid may mask cyanocobalamin deficiency and vice versa.
The presence of ascorbic acid in the blood and urine may cause false high or low glucose readings in some blood and urine glucose testing systems.

Biotin may interfere with laboratory tests that are based on a biotin/streptavidin interaction, leading to either falsely decreased or falsely increased test results, depending on the assay. The risk of interference is higher in children and patients with renal impairment and increases with higher doses. When interpreting results of laboratory tests, possible biotin interference has to be taken into consideration, especially if a lack of coherence with the clinical presentation is observed (e.g. thyroid test results mimicking Graves' disease in asymptomatic patients taking biotin or false negative troponin test results in patients with myocardial infarction taking biotin). Alternative tests not susceptible to biotin interference should be used, if available, in cases where interference is suspected. The laboratory personnel should be consulted when ordering laboratory tests in patients taking biotin.

Compatibility
Compatibility should be tested before mixing with other infusion solutions/emulsions (see sections 6.2 and 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

Some drugs may increase or decrease vitamin levels due to different interactions.

Drugs that increase vitamin levels include:
- Retinoids (e.g. bexarotene or acitretin) increase the risk of hypervitaminosis A (see sections 4.3 and 4.4).

Drugs that decrease vitamin levels include:
- Drugs interfering with vitamin D metabolism, including antiepileptics (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin and primidone), antineoplastics (e.g.anthracyclines, taxanes), rifampicine, glucocorticoids, efavirenz, zidovudine and ketoconazole may increase vitamin D inactivation rate

- Pyridoxine antagonits including cycloserine, hydralazine, isoniazid, penicillamine, phenelzine and theophylline and certain enzyme-inducing anticonvulsants (e.g. phenytoin or carbamazepine) may increase pyridoxine requirements
- Ethionamide can cause pyridoxine deficiency
- Folic acid antagonists (e.g. methotrexate, pyrimethamine), enzyme inducing anti-epileptic drugs (e.g. phenytoin, fosphenytoine carbamazepine, primidone) and high doses of tea catechins may cause folate deficiency by blocking the conversion of the inactive form to the active form of folic acid
- Treatment with rifampicine decrease the vitamin D concentration

Further interactions:

- Folic acid can interfere with effectiveness of some anticonvulsants, e.g. phenobarbital, phenytoin, fosphenytoin and primidone, leading to increased seizure frequency. High levels of folic acid may lead to increased cytotoxicity of fluoropyrimidine based chemotherapies.
- Deferoxamine: Increased risk of iron-induced cardiac failure due to increased iron mobilization by vitamin C supplementation (>500mg). For specific precautions, refer to deferoxamine product information.
- Nutratain contains vitamin A, which may lead to an increase in idiopathic intracranial hypertension when use in combination with medicines that can cause idiopathic intracranial hypertension (e.g. some tetracyclines)
- Nutratain contains vitamin K, which may weaken the effect of an anticoagulatory treatment with coumarin derivatives (e.g. acenocoumarol, warfarin, phenoprocoumon). Therefore, during treatment with anticoagulants of that type, careful monitoring of the blood coagulation factors (prothrombin time (PT)/ International Normalized Ratio (INR) should be more frequent.
- Tipranavir oral solution: contains 116 IU/mL of vitamin E, which is in excess of the daily recommended intake.

Interactions with additional vitamin supplementation:
Some medications can interact with certain vitamins at doses markedly higher than those provided with Nutratain. This should be taken into consideration in patients receiving vitamins from multiple sources. When applicable, patients should be monitored for such interactions and managed accordingly.

4.6 Fertility, pregnancy and lactation

Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing Nutratain.

Pregnancy
There are no or limited amount of data from the use of Nutratain in pregnant women.
Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
The use of Nutratain may be considered during pregnancy, if necessary, providing the indication and dosages are observed in order to avoid vitamin overdose.

The advised daily dose should not be exceeded as high doses of Vitamin A during pregnancy can cause malformations to the foetus.

Breast-feeding

Nutratain and it's metabolites are excreted in human milk.
Use of Nutratain is not recommended during breastfeeding because of the risk of vitamin A overdose in the neonate.

Fertility
No data available.

4.7 Effects on ability to drive and use machines

Nutratain has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

There have been rare reports of anaphylactoid reactions following parenteral multivitamin administration. Rare reports of anaphylactoid reactions have also been reported following large intravenous doses of thiamine mainly in patients predisposed to allergic reactions. However, the risk is negligible if thiamine is co-administered with other vitamins of the B group.

Listing of undesirable effects
Undesirable effects are listed according to their frequencies as follows:

Very common:	(1/10)
Common:	(1/100 to 1/10)
Uncommon:	(1/1 000 to <1/100)
Rare:	(1/10 000 to <1/1 000)
Very rare:	(<1/10 000)
Not known:	(cannot be estimated from the available data)

Gastrointestinal disorders
Not known: Nausea, vomiting, diarrhoea

General disorders and administration site conditions
Not known: Injection site reactions, e.g. burning sensation, rash

Immune system disorders
Not known: Hypersensitivity up to anaphylactic shock

Investigations
Not known: Transaminases increased, alanine aminotransferase increased, total bile acids increased, gamma-glutamyltransferase increased, glutamate dehydrogenase increased, blood alkaline phosphatase increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The risk of overdose is particularly high if a patient receives vitamins from multiple sources or overall supplementation of a vitamin does not match the patient's individual requirements, or in patients with increased susceptibility to hypervitaminosis (e.g. patients with hepatic or renal impairment) (see section 4.4).

Symptoms of overdose:
Most frequent overdoses of multivitamins are associated with nausea, vomiting, and diarrhea. Furthermore, acute or chronic overdose of vitamins can cause symptomatic hypervitaminosis with symptoms such as:
- **Vitamin A:** dry, peeling skin and signs of increased intracranial pressure; liver injury may cause jaundice and ascites
- **Vitamin C:** calcium oxalate crystals may cause acute renal failure or chronic nephropathy
- **Vitamin D:** hypercalcaemia
- **Vitamin E:** nausea, headache, weakness
- **Vitamin K:** may cause coagulation disorders
- **Vitamin B_6:** peripheral neuropathy
- **Vitamin B_2:** may produce yellow perspiration
- **B-Vitamins:** may intensify the yellow colour of urine

Treatment:
Treatment of the vitamin overdosage usually consists of withdrawal of the vitamin and other measures as clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: IV solution additives, vitamins
ATC code: B05XC
Vitamins are an indispensable component of nutrition. They serve to maintain the integrity of the organism and the body functions.
Parenterally administered vitamins prevent the clinical sequelae of vitamin deficiency in situations where food cannot or must not be taken up orally.

5.2 Pharmacokinetic properties

Absorption
The active substances contained in the medicinal product are physiological components of the organism and are 100 per cent bioavailable as a result of administration by the intravenous route.

Distribution and Metabolism
The vitamins are distributed in the body in the same manner as vitamins taken up with oral food. The same applies for all metabolic processes.

Excretion
Fat-soluble vitamins are primarily stored in the liver and adipose tissues. With the exception of vitamin K, fat-soluble vitamins are generally excreted more slowly than water-soluble vitamins, and vitamins A and D can accumulate and cause toxic effects in the body. Vitamin K accumulates mainly in the liver but is stored in the body only for short periods of time. Water-soluble vitamins, such as

Vitamin C and the B vitamins are stored in the body for only a brief period of time and are then excreted via urine.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Details are as follows:

a) Toxicity
The single-dose and repeat-dose toxicity of active ingredients is very low. The data available do not suggest any potential risk for humans.

b) Mutagenic or tumorigenic potential
No preclinical studies regarding the mutagenic or tumorigenic potential of Nutratain are available.
Mutagenic and carcinogenic effects of active ingredients are not to be expected under the conditions of clinical use.

c) Teratogenicity
No studies regarding reproductive and developmental toxicity of Nutratain are available.
Altered fetal development has been reported in studies testing high doses of single vitamins.

d) Reproduction toxicity
Studies of embryotoxicity have not been performed with Nutratain.
The matrix – so-called mixed micelles (glycocholic acid + lecithin) has been investigated.
Studies of embryotoxicity in rats and rabbits did not yield any results suggesting teratogenicity.
In rabbits, 10 fold the therapeutic dose led to spontaneous abortions. Administration of about 10-20 fold the therapeutic dose to rats during the peri- and postnatal period led to an increased mortality of the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Hydrochloric acid (for pH adjustment)
Sodium glycocholate
Soyphosphatidylcholine
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product should not be mixed with other medicinal products if compatibility and stability have not been demonstrated. See section 6.6 for more information.

If co-administration of drugs that are incompatible with Nutratain is necessary, administer via separate IV lines.

Additives may be incompatible with parenteral nutrition containing Nutratain.

Vitamin A and thiamine contained in Nutratain may react with bisulfites in parenteral nutrition solutions (e.g. as a result of admixtures) leading to degradation of vitamin A and thiamine.

An increase in pH of a solution may increase the degradation of some vitamins. This should be considered when adding alkaline solutions to the admixture containing Nutratain.

Folic acid stability can be impaired with increased calcium concentrations in an admixture.

6.3 Shelf life

- *unopened*
  2 years

- *after reconstitution and dilution*
  The reconstituted and diluted medicinal product should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). At room temperature (not above 25°C) it expires after 3 months.

6.5 Nature and contents of container

Vials of amber glass type I (Ph. Eur.) sealed with stoppers of bromobutylrubber, contents: 932 mg dry powder.
Available in packs of 5 and 10 vials
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for handling
Strict aseptic precautions must be followed during reconstitution and dilution of the product in a suitable solution/emulsion for infusion.
The content of a vial should be dissolved by adding 5 ml of a suitable solvent (water for injection or glucose solution 50 mg/ml or sodium chloride 9 mg/ml) and gentle shaking to dissolve the lyophilised powder. Do not use unless the reconstituted solution is clear and yellow-orange in colour. The reconstituted solution should be used immediately.

The powder must be completely dissolved before transferring to

- glucose 5% w/v
- sodium chloride 0.9% w/v
- lipid emulsion
- binary mixture for parenteral nutrition combining glucose, electrolytes and amino acids
- or ternary mixture for parenteral nutrition combining glucose, electrolytes, amino acid solutions and lipids

Mix the final solution thoroughly.
After addition of Nutratain to a parenteral nutrition solution, check for any abnormal color change and/or the appearance of precipitates, insoluble complexes or crystals.

This medicinal product should not be mixed with other medicinal products except those mentioned above unless compatibility and stability have been demonstrated.

Use only when the original seal is intact, yellow-orange cake or powder and the container is undamaged.

For single use only. Container and unused residues must be discarded after use.

7. MARKETING AUTHORISATION HOLDER

B. Braun Melsungen AG
Carl-Braun-Straße 1
34212 Melsungen, Germany

Postal address
34209 Melsungen, Germany

Tel.: +49-5661-71-0
Fax: +49-5661-71-4567

8. MARKETING AUTHORISATION NUMBER

PL 03551/0154

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 14/06/2018
Date of latest renewal: 14/04/2023

10 DATE OF REVISION OF THE TEXT

27/02/2026