# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

DAP® Penicillin.

Benzylpenicilloyl-octa-L-lysine 0.04 mg / Sodium benzylpenilloate 0.5 mg.

Powder and solvent for solution for injection/skin-prick test.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DAP® Penicillin is a medicinal product which consists of hapten derivatives of benzylpenicillin.

- Vial with benzylpenicilloyl-octa-L-lysine (major determinant) (BP-OL):
  The active substance is benzylpenicilloyl-octa-L-lysine. One vial contains 0.04 mg benzylpenicilloyl-octa-L-lysine as lyophilised powder.

- Vial with sodium benzylpenilloate (minor determinant) (MD):
  The active substance is sodium benzylpenilloate. One vial contains 0.5 mg sodium benzylpenilloate as lyophilised powder.

- Vial with 1.2 ml solvent for DAP® Penicillin for reconstitution and dilution (phosphate buffer).

One millilitre of reconstituted solution contains 0.04 mg benzylpenicilloyl-octa-L-lysine.

One millilitre of reconstituted solution contains 0.5 mg sodium benzylpenilloate.

**Excipient with known effect:**

One millilitre of reconstituted benzylpenicilloyl-octa-L-lysine/sodium benzylpenilloate solution contains 0.1530 mmol and 0.1545 mmol sodium, respectively.

One millilitre of reconstituted benzylpenicilloyl-octa-L-lysine/sodium benzylpenilloate solution contains 0.00415 mmol and 0.00415 mmol potassium, respectively.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection/skin- prick test.

White or off-white lyophilised powder.

The solvent for DAP® Penicillin for reconstitution and dilution is a transparent and odourless liquid.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

DAP® Penicillin is suitable for use in adults. Use in children and adolescents aged 2 to 17 years is restricted (see section 4.2 “Paediatric population” and section 4.4).

DAP® Penicillin is indicated for the diagnosis of hypersensitivity reactions of the immediate type to the penicillin components benzylpenicilloyl-octa-L-lysine and sodium benzylpenilloate.

Diagnostic assessment of a possible sensitisation to these components is done with skin prick tests or intradermal skin tests in cases where a type I allergy to beta-lactam antibiotics is suspected.

For correct diagnosis of type I allergy to beta-lactam antibiotics, the medical history of the patient must be accurately compiled. Beside skin testing with penicillin components as contained in the DAP® Penicillin, testing with other beta-lactam antibiotic reagents might be necessary, as DAP® Penicillin may fail to detect specific sensitisations to these other beta-lactam antibiotics.

It is recommended to perform skin tests earliest one month after complete healing of the skin reaction, but within one year as possible after the skin reaction had occurred. Skin tests should principally be performed during a symptom-free or clinically largely unobtrusive period.

If contraindications are present that may increase the risk of an anaphylactic reaction a waiting period must be observed, respectively the patient must be treated until a skin test can be undertaken. The washout phase of the medicinal substances that may inhibit the skin reaction towards the penicillin components contained in DAP® Penicillin must thereby be observed (see section 4.5).

## 4.2 Posology and method of administration

Posology

*Prick test*
In general for the prick tests, one drop of the undiluted test solutions is used.

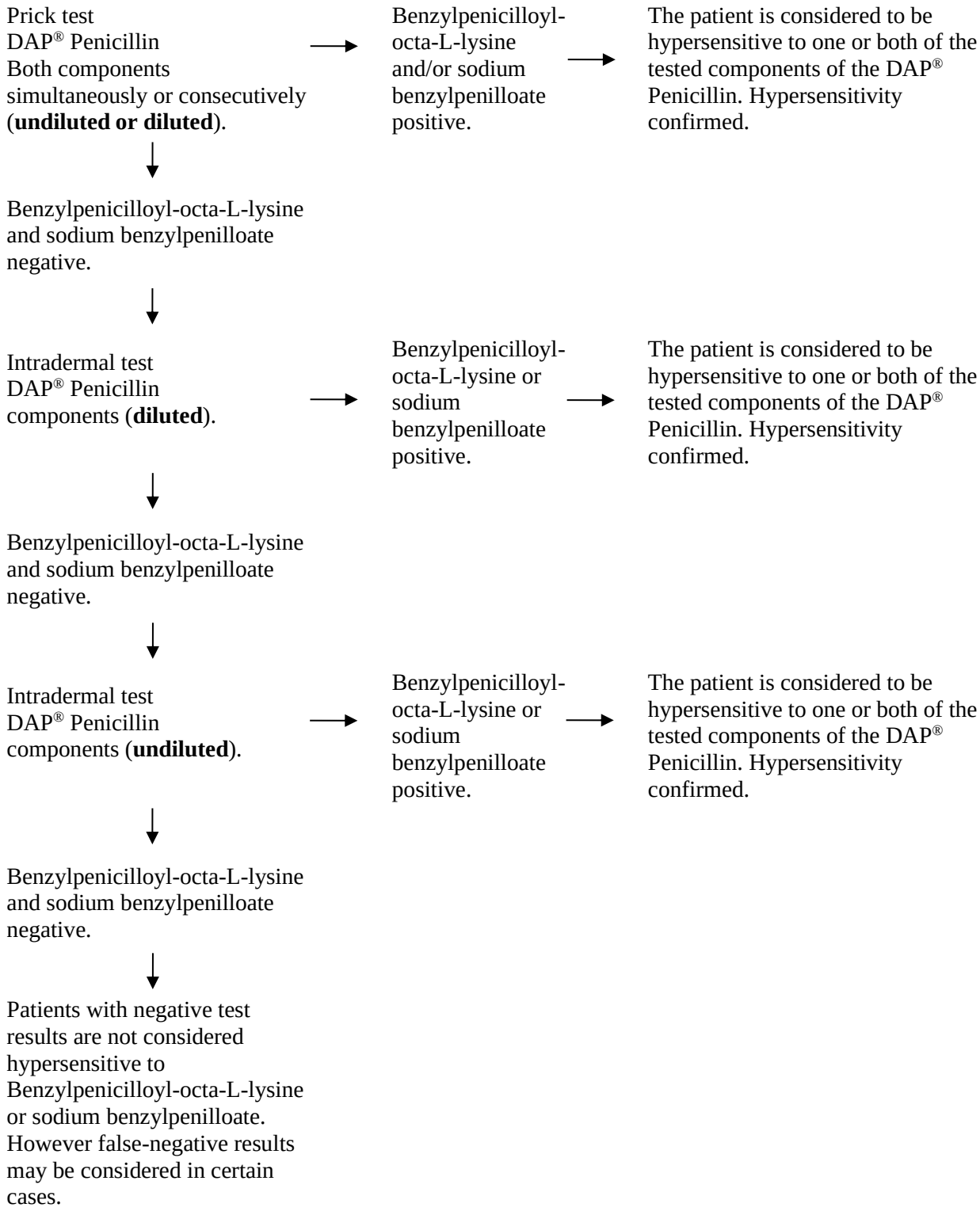
*Intradermal test*
In general for the intradermal tests, it is recommended to start with a 1:10 dilution of test solutions before continuing with undiluted test solutions. A volume of 0.02 to 0.05 millilitres of the test solutions is administered intradermally.

Based on clinical manifestation and severity of previous allergic reactions in patients and according to the assessment of the treating physician, proposed testing doses and testing regimen may be modified. In patients with a medical history of severe allergic reaction to beta-lactam antibiotics, or at high risk the intradermal skin tests should start at higher dilutions than 1:10 according to the assessment of the treating physician.

*Testing sequence*
Skin tests are commenced by examining skin reactivity using the prick technique. The prick tests with benzylpenicilloyl-octa-L-lysine and sodium benzylpenilloate should generally be performed simultaneously and in advance to the intradermal tests. Intradermal tests should be performed only when prick tests have proven negative. The following sequence of skin tests for evaluating immediate hypersensitivity reactions to penicillin determinants should be followed:

**Sequence for performing skin tests with DAP® Penicillin**

On the basis of the individual anamnesis of the patient and the individual risk assessment through the treating physician deviations can take place, which amongst others include a non-simultaneous application of the two test substances for the prick test or the dilution of the test substances for the prick test.




Tests with incrementally increasing concentrations of the test substances (for example 1:1000, 1:100, 1:10) can reduce the risk of a serious allergic reaction within the scope of the performance of a skin test.

Depending on the assumed pathomechanism, the severity of the occurred allergic reaction and the risk of the applied skin test method it should be decided whether the test substances in the skin test are to be administered simultaneously or consecutively.

In patients with an anamnesis of serious anaphylactic reactions the test substances for the prick test should principally be diluted and the two components should principally be used consecutively, not simultaneously.

*Special populations:*

*Elderly*

There is limited data on the use of DAP® Penicillin in elderly population.

*Paediatric population*

The safety and efficacy of DAP® Penicillin in children aged 0 to 24 months has not been established. Therefore DAP® Penicillin should not be used in these patients.

For children, and adolescents aged 2 to 17 years a similar mode of action of the DAP® Penicillin as for adults is expected. However, no data exist regarding appropriate dosages, injection volumes or wheal sizes for this patient population. Therefore the selection of dosages, dilution steps, injection volume and test sequence (simultaneous or sequential administration of test compounds) requires a thorough and critical assessment by the treating physician.

Besides such assessment, specific safety precautions as listed below should be followed:

- Skin tests and especially intradermal tests can be painful in children, especially infants and should be used with caution. The necessity for skin tests in children, respectively for repeated tests with increasing concentrations of the test substances should therefore be critically assessed in advance by the physician and carefully considered.
- *In vitro* tests for confirmation of specific Immunoglobulin E (IgE) antibodies against the penicillin components in DAP® Penicillin can be especially helpful in case of serious life-threatening oversensitivity reactions. This applies above all in situations in which no provocation test can be performed, respectively the skin test itself represents a possible hazard for the patient, for example with suspected anaphylactic reactions against the penicillin components in DAP® Penicillin. In these cases, an *in vitro* test for specific IgE antibodies should be available before the performance of a skin test. In the case of a positive *in vitro* test the performance of skin tests can be omitted. In the case of a negative *in vitro* test a skin test should be performed. A definite confirmation or exclusion of oversensitivity towards the penicillin components in DAP® Penicillin is not always possible solely on the basis of *in vitro* tests, however the risk assessment is facilitated thereby.

Method of administration

As systemic and even life-threatening reactions can occur as reaction towards skin tests, specialist clinical understanding is necessary for the performance of skin tests to be able to interpret the results and to prevent a possibly serious incorrect diagnosis.

Skin tests are generally safe, but systemic reactions can occur. Therefore, tests should be performed by physicians who have sufficient experience in diagnosis and treatment of anaphylactic reactions.

It is up to the physician’s individual benefit-risk-evaluation to perform the allergy skin tests under inpatient conditions.

For the treatment of anaphylactic reactions, the treating physician must have a corresponding emergency equipment available. Information on this can be found in the currently valid guideline on

"Acute therapy and management of anaphylaxis" from the Deutsche Gesellschaft für Allergologie und klinische Immunologie (DGAKI, German Association for allergology and clinical immunology) and other organisations.

The product must be reconstituted prior to use. For reconstitution of the major and minor determinant lyophilisates and dilution of test solutions prior to use, see section 6.6. Before performing the skin tests, vials containing the test solutions are allowed to stand for at least 10 minutes at room temperature.

Skin tests with DAP® Penicillin are performed on the inner side of the forearm.

*Prick test:*
Prepare the skin area and apply a small drop of each determinant with a 28 to 32G cannula at a distance of at least 2 cm. Also, 1% histamine dihydrochloride solution (10 mg/mL) as positive control and phosphate-buffered saline solution as negative control must be applied. The surface layer of the skin is punctured through the drop with a component specific lancet. Very little pressure is required to break the continuity of the epidermis. Excess liquid is removed immediately thereafter. Check the puncture site after 15 to 20 minutes.

The result is considered to be “positive” when the diameter of the wheal is more than 3 mm, or if it has an irregular, finger-like shape (pseudopod formation).

| **Largest wheal diameter** | **Skin test result** |
|---|---|
| Less than or equal to 3 mm | Negative |
| Larger than 3 mm | Positive |

If the prick test is “negative”, an intradermal test should be performed.

*Intradermal test:*
Prepare the skin area. Use a short 21 cannula and a 1 mL syringe specific for every component and dilution. Inject a volume of 0.02 to 0.05 millilitre of each determinant at the selected dilution intradermally into different sites at a distance of at least 2 cm and determine the diameter of the original wheal. Also, 0.1% histamine dihydrochloride solution (1 mg/mL) as positive control and phosphate-buffered saline solution as negative control must be applied.

Check the skin injection sites again after 15 to 20 minutes and determine the diameter of the resulting wheal.

The result is considered to be “positive”, if the difference in diameter between the original wheal and the resulting wheal is more than 3 mm.

| **Difference between resulting wheal diameter vs. original wheal diameter** | **Intradermal test result** |
|---|---|
| No increase | Negative |
| Less than or equal to 3 mm | Negative |
| Larger than 3 mm | Positive |

A skin test may produce a reaction even later than after 20 min. The treating physician must be contacted, if the skin test produces a reaction within 48 hours and 72 hours or even later up to weeks.

## 4.3 Contraindications

DAP® Penicillin must not be used:

- in cases of hypersensitivity to any of the excipients listed in section 6.1.
- in the presence of a pathological condition affecting the surface of skin to be used for the skin tests, any other pathological conditions significantly affecting the patient's general well-being.
- if the patient is suffering an acute allergic reaction caused by any allergen.
- if the patient is taking antihistamines, corticosteroids, chromones or other medicinal products that have an anti-allergic effect (see section 4.5).
- if, for therapeutic reasons, beta-blockers (also in eye drops) or ACE inhibitors are being taken (see section 4.5).
- In patients with uncontrolled or only partly controlled bronchial asthma, the test must not be performed.

## 4.4 Special warnings and precautions for use

Skin tests during pregnancy and breastfeeding are not recommended due to the additional risk of a possible anaphylactic reaction, but the decision in each case is at the discretion of the physician responsible for performing the test, who must decide when best to perform the diagnostic skin tests after appraisal of the individual benefit-risk ratio (see section 4.6).

There are insufficient data on the use of this diagnostic kit in children and adolescents. Non-irritant concentrations of the test substances, injection volumes for intradermal tests and optimal size of wheals in intradermal diagnostic tests are unknown for children and adolescents. The use of skin testing in children should be determined by the healthcare professional, after careful consideration of dosage (dilutions/titrations, steps, injection volume) and sequence of application of the different substances or substance-concentrations.

As adrenalin, respectively epinephrine is recommended for the treatment of severe adverse allergic/anaphylactic reactions, the respective contraindications must be observed. Adrenalin/Epinephrine and emergency equipment must always be immediately available.

After the test, the patient must remain under medical observation for at least 30 minutes.

Sodium:
After reconstitution, this medicinal product contains less than 1 mmol (23 mg) sodium per millilitre, i.e. essentially 'sodium-free'.

Potassium:
After reconstitution, this medicinal product contains less than 1 mmol (39 mg) potassium per millilitre, i.e. essentially 'potassium-free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Antihistamines, corticosteroids, chromones and other medicinal products with antiallergic activity may interfere with the skin test results. If possible before the performance of skin tests these medicinal products should no longer be administered within the time range that is specified by the respective manufacturer as being the effect duration.

The following time intervals that were taken from the guideline "Skin tests for the diagnosis of immediate allergic reactions" from the Deutsche Gesellschaft für Allergologie und klinische Immunologie (DGAKI) serve as recommendation for the discontinuation of the respective medicinal substances before the skin tests.

| **Medicinal substance** | **Duration of the interruption before application of the skin test** |
|---|---|
| Antihistamines (for the treatment of allergies) | > 3 days |
| Antihistamines with long effective duration (Astemizole) | > 8 weeks |
| Mast cell stabiliser Ketotifen | > 5 days |
| Tricyclic antidepressants | > 2 weeks |
| Neuroleptic Promethazine | > 5 days |
| Corticoids to be applied locally (e. g. ointment preparations) | > 1 week |
| Corticoids at a dosage < 50 mg Prednisolone equivalent per day | > 3 days |
| Corticoids at a dosage > 50 mg Prednisolone equivalent per day | > 1 week |
| Corticoids with long-term application at a dosage > 10 mg Prednisolone equivalent per day | > 3 weeks |

Oral and topical use of beta-blockers as well as the oral use of ACE inhibitors must be discontinued 48 hours before the skin tests, always in consultation with the treating physician and with due monitoring of the patient’s blood pressure.

If the patient is receiving allergen immunotherapy, the skin tests should be performed at least one week after administration of the last dose of immunotherapy. Similarly, the period between the skin tests and administration of an immunotherapy dose should be 2-3 days.

In the hours before and after the tests, the patient is required to abstain from alcohol consumption, intense physical activity and hot baths/showers.

## 4.6 Fertility, pregnancy and lactation

Pregnancy and breastfeeding

The performance of skin tests during pregnancy and breastfeeding represents a risk. Therefore, this medicinal product should only be applied during pregnancy and breastfeeding if an important therapeutic decision depends on the test result and with high probability a systemic anaphylactic reaction is not to be expected on the basis of the overall circumstances.

Fertility

No reproductive or developmental toxicity studies have been performed. No data are available on the reproductive or developmental toxicity of benzylpenicilloyl-octa-L-lysine and sodium benzylpenilloate.
Reproduction studies in mice, rats and rabbits revealed no indications of impaired fertility or harm to the foetus with penicillin G.

## 4.7 Effects on ability to drive and use machines

DAP® Penicillin has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Adverse reactions may occur immediately or hours after administration.

Due to product composition no skin infections are expected.

Usually, a skin prick test causes no problems; however, due to its mechanism of action, it can cause the following IgE-mediated adverse reactions:

Local reactions
Erythema, oedema or inflammation, with or without pruritus at the puncture site. These usually manifest after 10 to 60 minutes and may persist for several hours.

Moderate systemic reactions
Erythema and pruritus, which may progress to generalised urticaria or an exanthematous condition, with ocular or nasal symptoms and angioedema. Onset of these symptoms is usually within a few minutes to 4-6 hours after the test.

Severe systemic reactions: anaphylaxis
Anaphylaxis may develop immediately or a few minutes after performing the skin tests. It usually manifests with typical symptoms, including the onset of pruritus of the hands and feet, as well as lingual and sublingual pruritus affecting the throat, as well as metallic taste. Anaphylaxis can lead to severe, rapid collapse affecting multiple organs and systems: e.g. circulatory collapse with marked hypotension, anxiety conditions and tachycardia, rhinorrhoea, laryngeal oedema with the development of dyspnoea, bronchospasm with dyspnoea, generalised pruritus, urticaria and angioedema, abdominal pain, nausea, vomiting and diarrhoea, impaired sphincter function, restlessness, seizures and loss of consciousness.

Paediatric population

The frequency, nature and severity of adverse reactions in children are likely to be the similar as in adults.

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 to via the national reporting system.

## 4.9 Overdose

DAP® Penicillin is administered for skin tests only.

With correct application of the skin test an overdose is very improbable. With incorrect application stronger allergic reactions can occur (see section 4.8). In such cases corresponding countermeasures are to be initiated by the treating physician.

Therefore, with the performance of all tests a so-called **anaphylactic shock** kit should be available for immediate application with a ready to use adrenaline injection.

Adverse reactions can still occur hours after the allergen application; in case of doubt and especially with occurrence of systemic reactions the patient should immediately consult his or her physician.

For the treatment of anaphylactic reactions, the treating physician must have emergency equipment available and have corresponding experience in the treatment of anaphylactic reactions. Information on this can be found in the currently valid guideline on "Acute therapy and management of

anaphylaxis" from the Deutsche Gesellschaft für Allergologie und klinische Immunologie (DGAKI, German Association for allergology and clinical immunology) and other organisations.

Regarding the treatment of anaphylactic reactions there are no differences in children and adolescents compared to adults.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tests for allergic diseases, ATC code: V04CL10

As a rule, penicillin can be inactivated or degraded in three ways: binding to proteins, biotransformation and elimination. Penicillin is metabolised in the liver into an inactive compound that is excreted; large proteins, normally present in plasma, can bind to penicillin.

Penicillin is predominantly (approximately 95%) metabolised by conjugation with endogenous proteins to a hapten penicilloyl component. This conjugate is called the major determinant. Other metabolites of penicillin make up 5% or less of the penicillin administered and, together with penicillin G, are known as minor determinants.

These newly formed determinants can, *in situ*, induce a type I immediate reaction (IgE-mediated) such as the one that can be triggered by the determinants in DAP® Penicillin.

At 18 Spanish study centres, a prospective multicentre clinical study was conducted. This prospective multicentre study with DAP® Penicillin was performed in adults. Efficacy was assessed by detection of positive skin tests in an allergic population and negative test results in a non-allergic population exposed to the medicinal product. Sensitivity and specificity, as well as negative and positive predictive values, were determined.

The study included 94 allergic patients and 79 healthy control subjects: the following table summarises the results:

| **Parameter** | **Results** | **95% CI** |
|---|---|---|
| **Sensitivity** | 60.64% | 50.23 - 71.05% |
| **Specificity** | 100% | 99.37% - 100% |
| **Negative predictive value** | 68.10% | 59.19 - 77.02% |
| **Positive predictive value** | 100% | 99.12% - 100% |

Paediatric population

The European Medicines Agency has waived the obligation of the Manufacturer to submit results of studies with DAP® Penicillin in children aged 0 to 24 months

See section 4.2 for further information on paediatric use.

For children from 24 months up to 18 years of age, safety and efficacy are assumed to be the similar as in adults based on literature data. The European Medicines Agency has therefore waived the request for separate studies in this pediatric age group.

## 5.2 Pharmacokinetic properties

No pharmacokinetics or biotransformation data are available.

## 5.3 Preclinical safety data

After single and repeated intradermal injections, benzylpenicilloyl-octa-L-lysine and sodium benzylpenilloate led to minor local reactions in rats, such as oedema and erythema at the injection sites, which usually regressed within a few days and caused corresponding histological lesions with minimal infiltration of inflammatory cells at the injection site. Benzylpenicilloyl-octa-L-lysine and sodium benzylpenilloate caused local reactions largely resembling those reactions caused by the non-irritating phosphate buffer, which is used as a transport medium. These reactions are attributable more to the method of administration and not to the substances used for the test. The doses and volumes of DAP® Penicillin administered for the single and multiple intradermal injections were equivalent to 120 and 40-fold the maximum recommended human dose (MRHD) based on mg/kg and mL/kg.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Vial containing the major determinant (BP-OL)
Mannitol

Vial containing the minor determinant (MD)
Mannitol

Solvent for DAP® Penicillin for reconstitution and dilution:
Sodium chloride
Potassium dihydrogen phosphate
Disodium hydrogen phosphate dihydrate
Potassium chloride
Water for injections

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

3 years.

*After reconstitution*

After reconstitution, store in a refrigerator (2°C-8°C). Do not freeze.

The stability of the reconstituted medicinal product has been demonstrated for 14 days at 2°C-8ºC.

*After dilution*

Dilutions of the reconstituted medicinal product have to be used immediately after preparation. Remaining or unused diluted material has to be discarded.

## 6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

Type I amber glass vials with rubber stoppers and a coloured aluminium flip-off cap.

**Each pack contains:**
3 vials each containing 0.04 mg of major determinant (BP-OL). Red label and cap.
3 vials each containing 0.5 mg of minor determinant (MD). Yellow label and cap.
12 vials each containing 1.2 ml with solvent for DAP® Penicillin. Grey label and cap.

### 6.6 Special precautions for disposal and other handling

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

Reconstitution of the medicinal product

The product must be reconstituted prior to use. Under sterile conditions and using a sterile syringe and cannula, 1 mL of solvent is withdrawn from each of a vial and added to the corresponding vial containing the lyophilised powder of the major determinant (BP-OL) and the minor determinant (MD), respectively. Shake vigorously during at least 7 seconds, until each lyophilizate has completely dissolved.

The reconstituted solution is transparent, colourless and odourless.

*Preparation of dilutions of the medicinal product*

For intradermal use, dilutions must be made. Dilutions should be prepared under the appropriate aseptic conditions.

- For the preparation of a 1:10 dilution of the reconstituted solution containing the major or minor determinant, 0.13 ml will be withdrawn from the vial with the reconstituted solution of the major or minor determinant with a sterile syringe and cannula and added to a vial containing 1.2 ml of the solvent. The resulting total volume in the vial containing the 1:10 dilution is 1.33 ml.
- For the preparation of a 1:100 dilution, 0.13 ml will be withdrawn from the vial containing the 1:10 dilution with a new sterile syringe and cannula and added to a vial containing 1.2 ml of the solvent. The resulting total volume in the vial containing the 1:100 dilution is 1.33 ml.

The preparation of further dilutions of the reconstituted solution containing the major or minor determinant, e.g. 1:1000 or 1:10000, will be performed in the same described way.

A total of 12 vials each containing 1.2 ml of solvent are available in a package. Since each package contains 3 vials with the major determinant and 3 vials with the minor determinant, and since 1 vial with solvent is needed for reconstitution of each lyophilizate, a total of 6 vials with solvent will be needed for reconstitution of the lyophilizates. Therefore, a total of 6 vials with solvent will be available for dilution.

For information on dilution series, see section 4.2.

## 7. MARKETING AUTHORISATION HOLDER

## 8. MARKETING AUTHORISATION NUMBER(S)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT

July 2021