Summary of Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

DAP® Penicillin, 0.04mg/0.5mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DAP – Penicillin is a drug compounded by hapten derivatives of Benzylpenicillin.

- Vial with the PPL (major determinant):
  The active substance is Benzylpenicilloyl octa-L-lysine. One vial contains 0.04 mg of Benzylpenicilloyl octa-L-lysine as lyophilised powder.

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

- Vial with Reconstitution solvent (phosphate buffer)

  For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

Lyophilised white or almost white powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DAP Penicillin is used for the Diagnostic assessment of allergic, sensitization, or type I hypersensitivity conditions, in those cases where an allergy to beta-lactam antibiotics is suspected, by means of skin testing (prick test and intradermal reaction).

4.2 Posology and method of administration

Posology

Skin tests with DAP should be started by studying the skin reactivity by means of the skin prick test technique. The use of the intradermal testing should only be started when the skin prick test have yielded negative results.

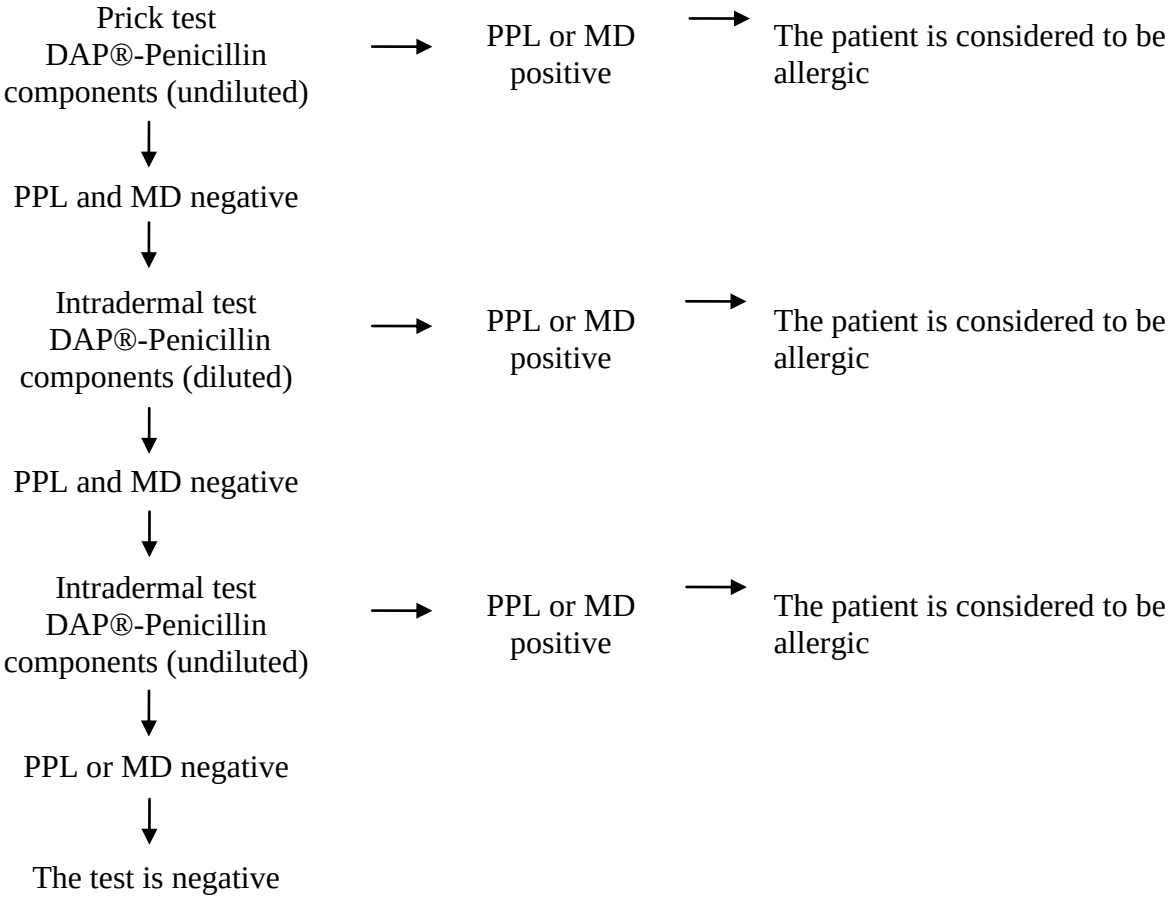
In a preventive way, it is recommended to apply a series of dilutions, 1:100 and 1:10, before performing the intradermal testing with the major determinant (PPL) and/or the minor determinant (MD).

In those patients whose symptoms are congruent with a severe reaction or present a high risk, skin testing should be started with 1:1000 dilutions.

The dilutions should be done under the appropriate required aseptic conditions and using the solvents that may be ordered.

It is recommended to follow the algorithm for the assessment of sensitivity to Penicillin determinants by skin testing:

Algorithm performing skin tests with DAP®



Method of administration

Skin test is performed on the inner volar of the forearm.

The product must be reconstituted before administration. Under sterile conditions, and using a sterile syringe and needle, add 1 mL of the diluent to the vials containing the lyophilized powder. Shake it slightly.

Prick test:
Prepare the skin surface, and apply a small drop of each determinant separated at least 2 cm using a sterile28-32 G needle. The superficial layer of the skin is pierced with a lancet. Very little pressure is required to break the epidermal continuity. After 15-20 minutes, observe the puncture area.

The result is considered 'Positive' if the diameter of the wheal is over 3 mm, or if it has an irregular, finger-like shape (pseudopod formation).

Major Wheal Diameter	Skin Test Result
Less than or equal to 3 mm	Negative
Greater than 3 mm	Positive

If the puncture test is negative, an intradermal test may be performed.

Intradermal test:
Prepare the skin area. Use a 28-32 G, short bevel needle with a 1 ml syringe. Inject 0.02-0.03 ml of each determinant at the chosen dilution intradermally.

Measure the wheal formed.

After 15-20 minutes, observe the puncture area again:
- The test is considered 'Positive' when the difference between the initial diameter of the wheal and the induced diameter is greater that 3 mm.
- The test is considered 'Negative' if no increase in size of original bleb is observed.

4.3 Contraindications

Do not use DAP - Penicillin in case of:

- A pathological condition of the skin surface area that will be used for skin testing, as well as any other pathological condition affecting considerably the general well being of the patient.
- During the course of an acute allergic reaction induced by any type of allergenic substance.
- Antihistamines, corticosteroids, cromones, and in general any type of medication presenting an anti-allergic collateral activity. These medications should be withdrawn at least one week before performing the skin assessment.
- The therapeutic use of beta-blockers or ACE inhibitors, which should

be withdrawn 48 hours before the tests and always in agreement with the prescribing physician and with blood pressure control.

- The administration of adrenalin, in case of the induction of a secondary allergic reaction.
- Pregnancy, breastfeeding, and generally, being under six years of age, constitute contraindications for the performance of cutaneous tests; however, it should always be left to the specialist's discretion, who must determine the convenience of, and the best timing for the diagnostic cutaneous examination on the basis of the risk-benefit required by each specific situation.

4.4 Special warnings and precautions for use

Skin testing during pregnancy is not recommended due to the additional risk from eventually inducing an anaphylactic reaction.

There is no sufficient evidence for the use of this diagnostic kit in pediatric population.

After skin testing, the patient should remain under supervision for at least 30 minutes.

It is necessary that the patient avoids taking alcohol, doing intense physical activity, and having hot bathing or showering the hours before and after the skin tests.

Should the patient be on allergen immunotherapy, skin tests ought to be performed with at least a one-week interval since the administration of the last immunotherapy dose. Similarly, the interval between the skin tests and the administration of an immunotherapy dose should be 2-3 days.

4.5 Interaction with other medicinal products and other forms of interaction

Antihistamines, corticosteroids, cromones and, in general, any other medication having a collateral antiallergic activity may interfere with the results yielded by the skin tests. In the particular case of oral antihistamines, their administration must be withdrawn one week before the skin testing.

The use of beta-blockers or ACE inhibitors must be withdrawn 48 hours before skin testing, always in agreement with the prescribing physician and with appropriate control of the blood pressure of the patient.

If the patient is following an immunotherapy treatment, see section 4.4 Special warnings and precautions for use.

4.6 Fertility, pregnancy and lactation

Pregnancy and breastfeeding

Pregnancy and breastfeeding represent a risk for skin testing, although the specialist's judgment will determine the convenience and proper time of performing the skin tests according to the risk-benefit ratio of each particular situation.

4.7 Effects on ability to drive and use machines

There are no reports regarding the effect on the ability to drive or use tools or machinery, so no special precautions are required.

4.8 Undesirable effects

Adverse reactions should appear immediately or hours after the administration. They are clasified as follows:

Local reactions

Such as erythema, edema, or inflammation, with or without pruritus, on the puncture area. It usually appears after 10 to 60 minutes and persists for several hours.

Moderate systemic reactions

Such a large-size papules, erythema, and pruritus, which may reach a generalised urticaria or exanthematic condition, with the presence of oculo-nasal symptoms and Quincke's edema. The appearance of symptoms usually takes place between a few minutes and 4-6 hours after the test.

Severe systemic reactions: anaphylaxis

Anaphylaxis may develop immediately and sequentially a few minutes after performing the cutaneous test. It usually exhibits prior standard symptoms, which involve the appearance of palmar and plantar pruritus, as well as pruritus above and below the tongue, which also affects the throat and leads to an intense, rapid collapse that affects several organs and systems: vascular collapse with marked hypotension, nasal congestion, laryngeal edema and bronchospasm; Generalized pruritus, urticaria and angioedema, abdominal pain, nausea, vomiting, and diarrhea; Metrorrhagia, tinnitus, vertigo, sphincter relaxation, seizures, and loss of consciousness.

4.9 Overdose

DAP- Penicillin is only administered for skin testing.

In case of accidental overdosing or incorrect performance of the skin tests, usually a vessel injury and therefore endovenous administration, an adverse reaction may occur, with a varying degree of importance, including anaphylaxis. Management of adverse reactions is described as below:

<u>Management of Local reactions</u>

Normally, it do not require pharmacological treatment, although it is advisable to use oral antihistamines and/or topical corticoid creams when the induration persists and its diameter is greater than 5 cm. Only in the event of severe local reactions is it advisable to use a tourniquet above the cutaneous test site and infiltrate the adjacent area with adrenaline S.C.

Management of Moderate systemic reactions
A tourniquet must be placed above the test site and pharmacological treatment must be started immediately. In those cases in which urticaria and Quincke's edema develop, administer antihistamines I.V., in addition to corticoids I.V. (i.e. prednisolone). If necessary, subcutaneous administration of adrenaline on the test site, which may be repeated every 15 minutes as well as bronchodilating aerosols and slow theophylline I.V.

The patient's blood pressure and pulse must be constantly monitored.

Management of Severe systemic reactions: anaphylaxis
Treatment involves placing a tourniquet above the test site and immediate subcutaneous or intramuscular administration of adrenaline on the site adjacent to the test site, which may be repeated every 15 minutes if necessary. Administration of antihistamines by oral or intramuscular route, as well as high doses of corticoids (i.e. prednisolone) by intravenous route, is mandatory in the case of considerable effects and edema. If respiratory compromise, in the form of severe or refractory bronchospasm, exists or co-exists, sympathomimetic bronchodilators and intravenous aminophylline must be administered. Administration of oxygen and electrolytic solution fluid therapy must be considered. Intubation or tracheotomy under certain circumstances and resuscitation in the event of circulatory failure must be anticipated for immediate action.

The patient's blood pressure and pulse must be constantly monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

In general, Penicillin may be inactivated or decayed by three ways: binding to proteins, metabolism, or excretion. Penicillin is metabolized in the liver to an inactive compound that is excreted; big proteins normally found in the plasma may bind to Penicillin.

Penicillin is a molecule containing an unstable and very reactive bound β-lactam-amide. Penicillin decay occurs in several ways: the β-lactam ring and its amide bound get opened under certain conditions, leading to a great variety of molecules, such as the penicilloic acid, penicillamine, and penilloaldehyde, among others, which are created through a wide range of unstable intermediate molecules such as the penillic acid, the penicilloic acid, and the penicillenic acid.

In humans, Penicillin may be metabolized into penicilloic acids. The amount of degradation of a series of Penicillin through both routes, hydrolysis of β-lactams and elimination of the side chain, has been identified in humans. On the other hand, some benzylpenicillin derivatives react in an irreversible manner mainly with amino lysine groups of the proteins to form haptenic groups benzylpenicilloyl-amine. Other haptenic groups are formed to a lesser extent. It may be considered that the benzylpenicillins may react to form haptenic benzylpenicilloyl groups though a reaction of direct aggregation of the β-lactam carbonyl to the lysine ε amino-terminals present in the proteins.

Penicillin is mainly (approximately 95%) metabolized in a haptenic penicilloyl fraction conjugated to endogenous proteins. This conjugate is known as the main determinant factor. Other Penicillin metabolites represent 5% or less of the Penicillin administered and, together with Penicillin G, are collectively known as the minor determinants.

These newly formed determinants may lead *in situ* to a type I immediate hypersensitivity response (IgE-mediated), as the one induced by the determinants contained in DAP- Penicillin.

5.2 Pharmacokinetic properties

There are no available data on pharmacokinetics and metabolism.

5.3 Preclinical safety data

The two determinants contained in the product DAP – Penicillin are compounds to which any human being having received treatment based on Penicillin has been exposed to. It is therefore considered that the clinical experience on the exposure to these compounds is vast, even at high doses and for prolonged treatments, so that this is an argument strong enough for not considering necessary to assess the direct systemic effects associated with these compounds, that is to say, their effects on internal organs. By contrast, the local effects at the injection site as well as those associated to an immunological reaction after their use have to be the focus of the pre-clinical evaluation.

So forth, the studies have been carried out. The first one assesses the unspecific irritating capacity, the second one studies acute toxicity, and the third one the toxicity from repeated doses, both through the intradermal route in rats.

Unspecific irritating capacity:
"Evaluation of the acute eye irritation/corrosion potential of two penicillin metabolites in female New Zealand White rabbits"

The results of this study did not show any sign of irritation and/or corrosion in the animals submitted to the metabolites; no lesions were observed in the necropsies either.

Acute toxicity study

"Acute toxicity of two combined penicillin metabolites after intradermal administration to male and female Sprague Dawley rats".

The aim of this study was to assess the acute toxicity and local tolerability after intradermal administration of the two allergenic determinants at full doses (maximum intradermal volume possible).

Study on the Toxicity to Repeated Doses for 4 weeks

"30-day toxicity evaluation after repeated intradermal administrations of two combined penicillin metabolites to Sprague Dawley rats".

The aim of the study was to assess the toxicity and local tolerability for 30 days after intradermal administration of repeated doses (days 1, 15 and 29) of the two allergenic determinants, PPL and sodium benzylpenilloate.

The control group animals were inoculated with the same volume of the vehicle at two injection sites, one at each side of the animal's back.

As indicated in the acute toxicity study, the two allergenic determinants, PPL and sodium benzylpenilloate, were administered reconstituted in a phosphate buffer at a final concentration of 0.04 mg/mL (PPL) and 0.5 mg/mL (sodium benzylpenilloate).

The follow-up of the clinical symptoms was carried out until the end of the study, with a main focus on local reactions (erythema and edema). Six animals in each group were sacrificed the next day of the last administration, whereas the remaining ones were observed for an additional 14-days period to assess the reversibility of the possible adverse reactions.

It is important to note that, in order to demonstrate the product's safety, both studies were performed under the extreme conditions of administration in humans. In humans, the skin reactivity study is started with the *prick-test*, and the intradermal administration is only carried out in case of a negative result with the *prick-test*, since inoculating the product at the dermis level by have an irritating effect. On the other hand, a maximum of two intradermal administrations ought to be done, and the volume administered with the intradermal test would be 0.02-0.05 mL.

In the acute toxicity study, the maximum possible volume was inoculated intradermally and thus, the maximum viable dose, which represents 200 times more than the maximum dose to be administered in humans, expressed in mg/Kg, and the volume administered at each inoculation site was the maximum recommended in humans (0.05 mL). In the study of toxicity with repeated doses, the volume administered at each inoculation site was also the maximum recommended in humans, and the dose of each one of the allergenic determinants administered at each one of the

administrations was 57 times more than the maximum dose recommended in humans, expressed in mg/Kg.

Moreover, in this case, a total of three intradermal administrations were carried out, one more than the number of administrations recommended in humans.

It should be noted, that the administration route in both studies was the intradermal route, which represents the worst-case scenario of the likely administration in humans.

Conclusions
The intradermal administration of PPL and sodium benzylpenilloate in rats, under the study conditions, did not elicit relevant signs of toxicity and it induced local reactions similar to those observed in the control group with the vehicle, and they were therefore attributable to the administration method rather than to the inoculated product. It is considered that the results yielded by the pre-clinical studies adequately support the safety of PPL and sodium benzylpenilloate for their administration in humans.

There are no studies with DAP - Penicillin assessing a carcinogenic or mutagenic effect, or an effect on fertility.

Since the doses used in diagnosis are very much lower than the ones usually administered in a treatment with Penicillin, we may rely on the wide knowledge on the mutagenic innocuity of these determinants.

Given the fact that DAP - Penicillin is not used on a continuous manner, carrying out studies on its carcinogenesis is not necessary.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Vial with the major determinant:

Excipient	
Mannitol	20mg/vial

Vial with the minor determinant:

Excipient	
Mannitol	20mg/vial

Reconstitution vial:

Components	**mg/vial**
Vial with the reconstitution solvent	

Sodium chloride	8 mg
Dihydrogen potassium phosphate	0.2 mg
Disodium hydrogen phosphate di-hydrate	1.15 mg
Potassium chloride	0.2 mg
Water for injection q.s.	1 mL

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

Shelf-life after reconstitution

Store in a refrigerator (2°C – 8°C).

Chemical and physical in-use stability has been demonstrated for 15 days if stored at 5ºC±3ºC.

6.4 Special precautions for storage

Non- reconstituted vials (lyophilized powder): Store below 25º C.

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

6.5 Nature and contents of container

Type I amber colour glass vial with rubber stopper and flip off aluminium seal.

Each pack contains:

- 3 vials of the major determinant
- 3 vials of the minor determinant
- 12 vials with solvent for reconstitution

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.

7. MARKETING AUTHORISATION HOLDER

Diater Laboratorio de Diagnóstico y Aplicaciones Terapéuticas, S.A.

Avda. Gregorio Peces Barba 2 - Parque Tecnológico de Leganés
28918 Leganés -Madrid
Spain

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

To be completed nationally