Diater Laboratorio de Diagnóstico
y Aplicaciones Terapéuticas, S.A

Summary of product characteristics

DAP® Clavulanic
Powder and solvent for solution for injection/skin-prick test

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DAP Clavulanic 20 mg powder and solvent for solution for injection/skin-prick test.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One millilitre of solution for injection contains 20 mg of clavulanic acid (as potassium clavulanate).

Excipient(s) with known effect

One vial of reconstituted DAP Clavulanic 20 mg contains 0.1848 mmol (4.25 mg) of sodium.

For 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 (physiological saline solution) is a transparent, colourless, and odourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

DAP Clavulanic is used for the diagnostic assessment of allergy, sensitisation or type I hypersensitivity, in those cases where an allergy to potassium clavulanate is suspected, through skin testing (skin prick tests or intradermal skin tests).

4.2 Posology and method of administration

Posology

For the prick test, one drop of the undiluted solution is used.

To avoid risks, in case of patients with anamnesis of severe allergic reaction it is recommended that the intradermal tests be started with a series of lower concentrations (0.5 mg/mL and 5 mg/ml) before the intradermal tests are performed with the most concentrated, undiluted vial.

Dilutions must be made under aseptic conditions and using the supplied solvents. For intradermal tests, 0.02 - 0.05 ml of the respective solutions are administered intradermally.

The reconstituted solutions are transparent, colourless and odourless.

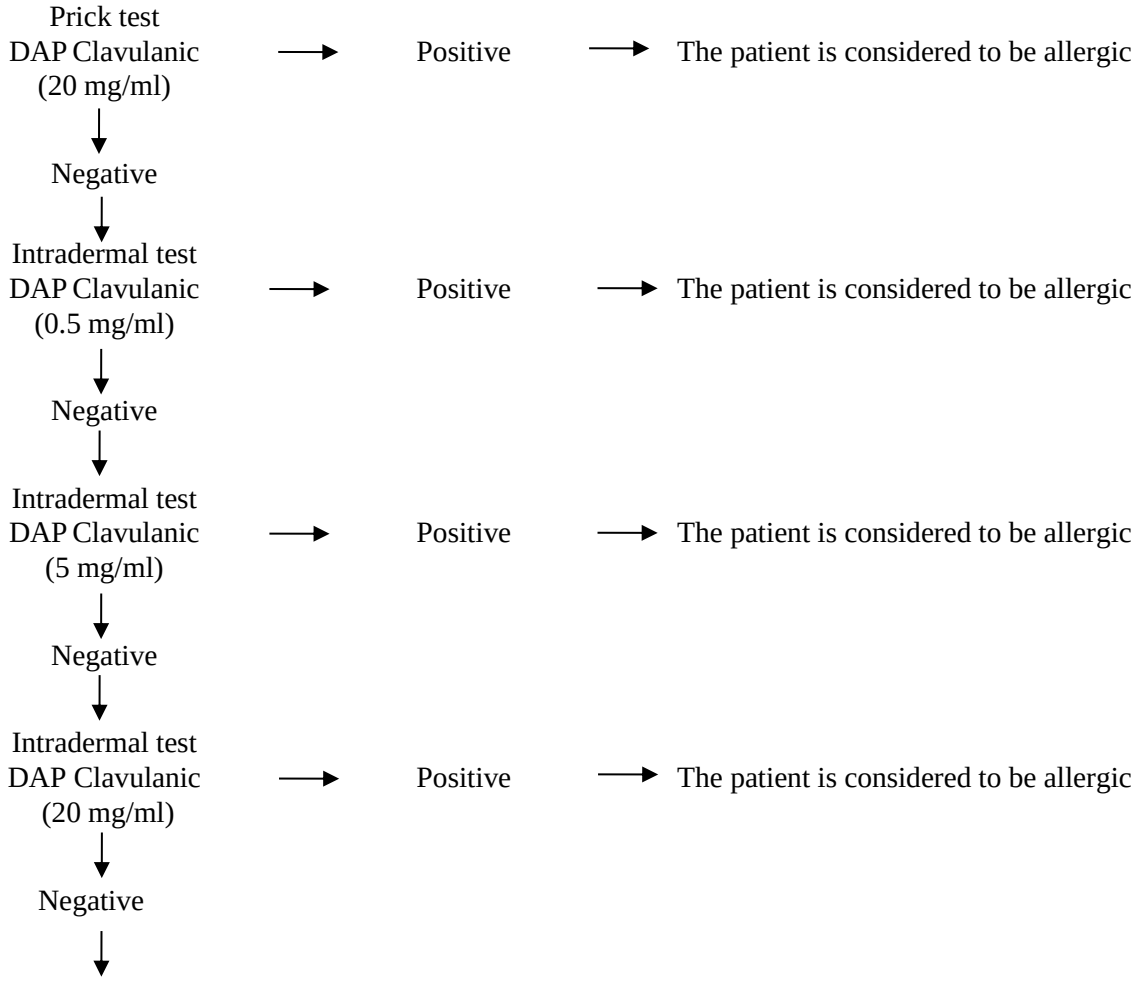
Method of administration

The skin test is performed on the inner side of the forearm.

The product must be reconstituted prior to use. For instruction on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Skin tests with DAP Clavulanic are commenced by examining skin reactivity using the prick technique. Intradermal tests should be performed only when skin prick tests have proven negative. It is recommended that the algorithm for evaluating sensitivity to potassium clavulanate by skin tests should be followed:

Algorithm for performing skin tests with DAP Clavulanic



The test is negative. It should be considered to complete the study with *in vivo/in vitro* tests if appropriate.

Prick test:

The skin surface is prepared and a small drop of potassium clavulanate and positive and negative controls, with a sterile 28-32G cannula at a distance of at least 2 cm. The surface layer of the skin is punctured through the drop with a lancet. Very little pressure at right angle is required to break the continuity of the epidermis. Check the puncture site after 15-20 minutes.

The result is considered to be "positive" when the diameter of the wheal is more than 3 mm compared with the negative control, with surrounding erythema, or if it has an irregular, finger-like shape (pseudopod formation). The result should not be assessed in case of bleeding.

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 can be performed.

Erythema and infiltration in the puncture site which appears from 30 minutes to 2 days after reading the test is considered delayed positive result.

Intradermal test:

The skin area is prepared. A short 28-32G cannula and a 1 ml syringe are used, and it is applied at 10-15 degrees. 0.02-0.05 ml dose of potassium clavulanate are injected intradermally at the selected dilution. The puncture site is checked again after 15-20 minutes:

The test is considered to be "positive" if the difference between the original wheal diameter, after intradermal reaction, and the resulting wheal after 20 minutes is more than 3 mm, with appearing of surrounding erythema. The result does not be assessed in case of injury.

The test is considered to be "negative" if no increase in the size of the original wheal is observed.

Erythema and infiltration, in the puncture site, higher than 5 mm until 72 hours is considered delayed positive result.

It is essential to observe and the patient control during the development of the skin response and up to the reading of the same, in order to act immediately on any adverse (local or systemic) reaction that may occur.

Paediatric population

There is no information about the use of DAP Clavulanic in the paediatric population.

4.3 Contraindications

DAP Clavulanic must not be used:

- In case 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, it is necessary to discontinue its use one week before skin testing (see section 4.5).
- if, for therapeutic reasons, beta-blockers or ACE inhibitors are being taken, these must be discontinued 48 hours before skin testing, always under the approval of the physician and with control of the blood pressure (see section 4.5).
- During pregnancy and lactation.
- In patients with uncontrolled or only partly controlled bronchial asthma.

4.4 Special warnings and precautions for use

There is no information about the security of DAP Clavulanic during pregnancy or breastfeeding (see section 4.6).

There are insufficient data on the use of this diagnostic medicinal product in children and adolescents.

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

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

In some cases, local irritative reactions have been described after the test (see section 4.8).

In the case of patients with a severe allergic reaction history to beta-lactam antibiotics, it is advisable to carry out several dilutions from 20 mg/ml vial, and prick test should be conducted at increasing concentrations, under physician criteria (see section 6.6.).

Sodium:
After reconstitution, this medicinal product contains less than 1 mmol (23 mg) sodium per millilitre, i.e., essentially 'sodium-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. These medicines must be discontinued at least one week before performing the skin tests.

Oral use of beta-blockers or 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.

4.6 Fertility, pregnancy and lactation

Pregnancy and breastfeeding

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.

Fertility

No reproductive or developmental toxicity studies have been performed. No data are available on the reproductive or developmental toxicity of potassium clavulanate.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile:

During the marketing period, the most frequent reactions reported with DAP Clavulanic are local reactions and generally consist of irritation, erythema, oedema or inflammation with or without pruritus at the injection site. They usually occur within 10 to 60 minutes after administration and may persist for several hours. They do not usually require pharmacological treatment, although the use of oral antihistamines and/or topical corticosteroids is recommended when induration persists, and its diameter is greater than 5 cm.

Possible systemic reactions are erythema and pruritus which may develop into generalised urticaria or an exanthematous condition with the presence of ocular or nasal symptoms and/or angioedema. Symptom onset usually occurs within minutes and in very rare cases may occur up to 4-6 hours after the test, which may require basic pharmacological treatment such as antihistamines and/or I.V. corticosteroids, bronchodilators and adrenaline if necessary.
Blood pressure and pulse should be constantly monitored in the patient.

Anaphylaxis may occur immediately or within a few minutes after the test. It usually manifests with typical symptoms such as palmar and plantar pruritus, as well as pruritus on the upper and bottom sides of the tongue also affecting the throat, as well as taste metallic. Anaphylaxis can lead to rapid and severe collapse affecting several organs and systems: vascular collapse with severe hypotension, anxiety and tachycardia, rhinorrhoea, laryngeal oedema with development of dyspnoea, bronchospasm with dyspnoea, generalised pruritus, urticaria and angioedema, abdominal pain, nausea, vomiting and diarrhoea, sphincter relaxation, restlessness, convulsions, and loss of consciousness.
Therefore, with the completion of all tests, an anaphylactic shock kit should be available for immediate application with an injection of adrenaline ready for use.

Tabulated summary of adverse reactions:

Immune system disorders
Anaphylactic reaction; anaphylactic shock.
Frequency: not known (cannot be estimated from the available data)

General disorders and administration site conditions
Irritation, erythema, oedema, inflammation, or pruritus at the injection site.
Frequency: not known (cannot be estimated from the available data)

Eye disorders
Lacrimation increased, eye pruritus, eye pain.
Frequency: not known (cannot be estimated from the available data)

Skin and subcutaneous tissue disorders
Erythema, pruritus, urticaria (including generalise), rash, angioedema.
Frequency: not known (cannot be estimated from the available data)

Vascular disorders
Hypotension.
Frequency: not known (cannot be estimated from the available data)

Description of selected adverse reactions

If the patient suffers of a significant adverse reaction as a result of the test, antiallergenic treatment should be considered.

In the post-marketing period severe anaphylactic reactions including anaphylactic shock have been reported. Therefore, as an important preventative measure, the initiation of treatment should be supervised by a physician (see section 4.2 and 4.4).

A physician should be contacted immediately in case of severe systemic reactions. In such cases, treatment should be discontinued permanently, or until recommended by the physician.

Paediatric population

There is no relevant data in the paediatric population.

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 national reporting system.

4.9 Overdose

DAP Clavulanic is administered for skin tests only.

In case of accidental overdose or incorrect skin test technique, adverse reactions may occur with varying degrees of severity, including anaphylaxis, usually as a result of injury to a blood vessel and subsequent endovenous administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Group V (Various), ATC code: V04CL. Tests for allergic diseases.

Clinical efficacy and safety

In a cross-sectional, multicentre study, 19 patients with hypersensitivity reaction after the administration of amoxicillin-clavulanic were diagnosed through skin tests and drug provocation tests. All patients resulted negative in skin tests with major and minor determinants of penicillin and with amoxicillin, and positive to clavulanic acid (Pineda *et al.* 2014).

In one study performed with 307 patients for diagnosis of allergy to penicillin, amoxicillin and clavulanic acid, DAP Clavulanic allowed for diagnosis of sensitization to clavulanic acid in 16 patients (Torres *et al.* 2010).

DAP Clavulanic in combination with the histamine release test allowed to diagnose hypersensitivity to clavulanic acid in a patient with a rash (Cerdá *et al.* 2013) and another patient with generalized urticaria (Cabañes *et al.* 2013) after the administration of amoxicillin-clavulanic.

Literature References

- Pineda F, Ariza A, Mayorga C, Perez I, Gonzalez-Mendiola R, Blanca N, Davila G, Cabañes N, Canto G, Laguna JJ, Senent C, Stahl Skov P, Palacios R, Blanca M. Diagnostic usefulness of histamine release test (HRT) and skin tests in IgE-mediated allergy to clavulanic acid. Clin Transl Allergy. 2014; 4(S3): O7.
- Torres MJ, Ariza A, Mayorga C, Doña I, Blanca-Lopez N, Rondon C, Blanca M. Clavulanic acid can be the component in amoxicillin-clavulanic acid responsible for immediate hypersensitivitiy reactions. J Allergy Clin Immunol. 2010; 125(2):502-5.
- Cerdá JC, Martorell C, Felix R, De las Marinas MD, Martorell A, Perez I, Iglesias-Sánchez JC, Pineda F, Stahl Skov P. *Passive transfer test in a patient with specific hypersensitivity to clavulanic acid*. Allergy 2013. 68; S97: 391. Póster 1066.
- Cabañes N, Perez-Perez I, Stahl Skov P, Pineda F, Marchan Martin E, Iglesias-Sánchez JC, Senent CJ. *Selective IgE mediated reactions in a patient to clavulanic acid demonstrated by histamine release test*. Allergy 2013. 68; S97: 393. Póster 1073

Paediatric population

There is no relevant data in the paediatric population.

5.2 Pharmacokinetic properties

There is no data on pharmacokinetic and metabolism.

5.3 Preclinical safety data

In one study for determination of non-irritant maximum dose in rats, 50 µL of potassium clavulanate in increasing concentrations were administered. The potassium clavulanate 20 mg/ml dose was considered as the non-irritant maximum dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Solvent for DAP Clavulanic reconstitution and dilution:
Sodium chloride.
Water for injections.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After reconstitution and dilution

After reconstitution and dilution, the shelf life is 24 hours. Store in refrigerator (2ºC-8ºC). Do not freeze.

6.4 Special precautions for storage

Store in refrigerator (2ºC-8ºC). Do not freeze.

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

6.5 Nature and contents of container

DAP Clavulanic is presented in Type I transparent glass vials, with rubber stopper and aluminium flip-off capsule.

Each pack contains:
- 4 vials containing 20 mg of potassium clavulanate.
- 12 vials containing 1.2 ml of solvent (physiological saline solution) for reconstitution and dilution.

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:
This medicinal product must be reconstituted prior to use. Under sterile conditions and using a sterile syringe and cannula, 1 ml solvent is added to the vial of lyophilised powder. The vial is shaken gently to homogenise the content. The vial is labelled with the text 20 mg/ml.

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, required aseptic conditions with diluents which can also be ordered separately.

- For the preparation of a 5 mg/ml dilution of the reconstituted solution, 0.4 ml will be withdrawn from the vial with the reconstituted solution 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 5 mg/ml dilution is 1.6 ml. The vial is shaken gently to homogenise the content. The vial is labelled with the text 5 mg/ml.
- For the preparation of a 0.5 mg/ml dilution, 0.13 ml will be withdrawn from the vial containing the 5 mg/ml dilution 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 0.5 mg/ml dilution is 1.33 ml. The vial is shaken gently to homogenise the content. The vial is labelled with the text 0.5 mg/ml.

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

March 2022.