SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Alustal, suspension for injection

2. Qualitative and quantitative composition:
1 vial contains 5 ml of suspension for injection:
• 0.01 – 0.1 - 1 or 10 IR/ml (standardized allergen extracts) or
• 0.01 – 0.1 - 1 or 10 IC/ml (non-standardized allergen extracts),
from the allergens, listed in the enclosed table /Annex I/.

Active substances: Allergen extract /Annex I/.
The active substance is a mannitoled freeze-dried allergen extract.

Excipients: see section 6.1

- IR (Index of Reactivity): An allergen extract has a titre of 100 IR/ml, if in a prick test performed using a Stallerpoint® it produces a wheal of 7 mm in diameter (geometric mean) in 30 subjects sensitised to the allergen in question. Skin reactivity in these subjects is simultaneously demonstrated by a positive response to a prick-test with codeine phosphate (9%) or 10 mg/mL dihydrochloride histamine.
- IC (Index of Concentration): An allergen extract has a titre of 100 IC/ml if its manufacturing parameters to the same dilution ratio than those of standardised extracts at 100 IR/ml from the same family, extracts taken as the reference.
When the family does not contain any standardised reference extract, the value 100 IC/ml corresponds to an extract dilution ratio established according to the medical experience.

When the allergen family does not contain standardized model extract, the value of 100 IC/ml corresponds to one extract that has a ratio of dilution, which is established by the medical practice.

3. Pharmaceutical form
Suspension for injection

4. Clinical particulars
4.1 Therapeutic indications
Type I allergies according to the Gell and Coombs' classification, which are manifested mainly as rhinitis, conjunctivitis, rhinoconjunctivitis and asthma (mild to moderate) either seasonally or annually.

4.2 Posology and method of administration

Conditions of administration:
Allergen immunotherapy (AIT) should be administered as soon as possible after the diagnosis. It is much more effective when started early.
AIT should be considered both for adults and children when indicated. Treatment may be undertaken in children from the age of 5 years old.

Posology and method of administration:
The posology does not change depending on the age, but may be adapted to the reactivity of the particular individual.
The treatment is conducted in two stages:

-initial treatment with progressive dose escalation;
-maintenance treatment with constant doses.

For seasonal allergies, it is recommended to start before the pollen season.
For perennial allergies, it is recommended to maintain the treatment all year round.

The following check should be performed before each injection:
- shelf life
- whether the vial corresponds to the prescription (composition, name of the patient, concentration). The vial should be shaken before use.
- whether the principles of asepsis are followed.
- "tuberculin" type of syringes of 1ml, graduated to 1/100, are used.
- the exactly determined dose is injected.
The patient should remain under observation of a doctor for 30 minutes after each injection. The patient should not do much physical activity in the remaining part of the day after the injection.

1. Initial treatment with progressive doses
Alustal is injected deeply subcutaneously once a week in a progressively incrementing dose until it reaches the maximum tolerable dose according to the following medicinal scheme.

Day	Injection	Vial (concentration)	Volume (in ml)	Dose (IR or IC)	Frequency
D0	1	0.01 IR/ml or 0.01 IC/ml (grey cap)	0.10	0.001	1 injection per week
D7	2		0.20	0.002	
D14	3		0.40	0.004	
D21	4		0.80	0.008	
D28	5	0.1 IR/ml or 0.1 IC/ml (yellow cap)	0.10	0.01	1 injection per week
D35	6		0.20	0.02	
D42	7		0.40	0.04	
D49	8		0.80	0.08	
D56	9	1 IR/ml or 1 IC/ml (green cap)	0.10	0.1	1 injection per week
D63	10		0.20	0.2	
D70	11		0.40	0.4	
D77	12		0.80	0.8	
D84	13	10 IR/ml or 10 IC/ml (blue cap)	0.10	1	1 injection per week
D91	14		0.20	2	
D98	15		0.40	4	
D105	16		0.60	6	
D112	17		0.80	8	

This medicinal scheme is a model and may be changed according to the patient's status and the possible reactions.

2. Maintenance treatment with constant doses

The maximum tolerable dose is given once every 15 days, each month or more, but the interval between two injections should not be more than 6 weeks.

Each medicinal scheme is a model and may be changed according to the patient's status and the possible reactions.

It is recommended to reduce the dose by half, at the time of change of vial and eventually during the pollen season.

Treatment duration

According to International consensus (WHO position paper 1998), AIT should continue for 3 to 5 years.

Treatment should be reassessed in absence of significant improvement of symptoms after the first pollen season (seasonal allergy) or after 1 year (perennial allergy).

Interruption of treatment

In case of treatment interruption or delay between 2 injections (not related to adverse reaction), the hereafter instructions should be followed:

PHASE	Treatment interruption since the previous injection	Posology
Initiation phase	2 weeks	Re-initiate with same volume and concentration as previous injection then continue the initiation phase
	2 weeks to 1 month	Re-initiate from 0,1 ml of the same concentration vial then continue the initiation phase
	More than 1 month	Re-initiate the initiation phase using concentration 10 fold lower (if possible *) then continue the initiation phase
Maintenance phase	Less than 6 weeks	No change in the injected volume and concentration
	More than 6 weeks	Re-initiate the initiation phase with 0.1 ml of the 1 IR/ml or 1 IC/ml vial until the maximum tolerated dose is reached. Then continue with maintenance phase.

* For patients treated with the lowest concentration, re-initiate the initial phase with the same concentration.

4.3 Contraindications

- Hypersensitivity to one of excipients (see list of excipients);
- Immune deficiency diseases or active forms of autoimmune disorder ;
- Malignant disease;
- Patients with uncontrolled or severe asthma (FEV1 < 70% of predicted value);
- Renal insufficiency

4.4 Special warning and precautions for use

Before starting the treatment, the patients subject to AIT should have their symptoms controlled in advance with the respective treatment, as necessary.

As systemic allergic reactions (that could be life-threatening when very severe) might occur after any allergen injection, it must be performed by a physician experienced in allergen immunotherapy and in conditions allowing immediate emergency treatment (including epinephrine).

Allergen immunotherapy in patients treated with tricyclic antidepressants and mono amine oxidase inhibitors (MAOIs) should be considered carefully.

Patients taking beta-adrenergic blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis. Specifically, beta-adrenergic blockers antagonize the cardiostimulating and bronchodilating effects of epinephrine.
Beta-adrenergic blockers should then be substituted with an alternative; if beta-adrenergic blockers are required and no effective substitute is available, treatment initiation should be evaluated carefully based on an individual risk/benefit assessment.

In case of occurence of symptoms following treatment administration such as intensive itching in palms of hand and soles of the feet, urticaria, mouth edema, pharyngeal edema leading to difficulty in swallowing, in breathing, or voice modification, nausea, vomiting, a physician has to be consulted immediately and the treatment should be discontinued.

In case of a febrile infection or of a recent asthma attack that is confirmed clinically and/or by expiratory peak flow measurement, the treatment should be suspended and restarted after improvement and after the advice of a physician experienced in allergen immunotherapy.

Respect of the AIT good practices is absolutely necessary to avoid possible incidents that are linked to:

- errors with the vials;
- errors with the dose;
- accidental intravascular injections;
- modifications of the interval between 2 injections;
- poor evaluation of the patient’s clinical condition.

Those risks should be considered before initiation of allergen immunotherapy.

The presence of sodium chloride should be taken into consideration in patients on a salt-free diet and children (one vial of 5 ml contains 45 mg of sodium chloride).

This medicine contains 4 mg aluminium (per 5 ml vial). Risk of accumulation of aluminium into tissues (central nervous system, bones) should be kept in mind, especially in case of renal insufficiency. Effects of long-term use of aluminium on immune system are unknown. Concomitant administration of medicine containing aluminium should be avoided (ex: antiacid drugs).

4.5 Interactions with medicinal products and other forms of interaction

No interaction studies have been performed.
No reactions with other drugs or medicines have been reported in clinical trials with Alustal.
In case of severe allergic reactions, use of epinephrine may be necessary. In patients treated with tricyclic antidepressants or Mono Amine Oxydase Inhibitors (MAOIs), risk of undesirable effects of epinephrine can be increased with possible fatal consequences. This risk would have to be considered prior to initiating allergen immunotherapy.

Clinical experience on vaccination during treatment with allergen immunotherapy is missing. Vaccination may be given without interrupting immunotherapy treatment, but only after medical evaluation of the general condition of the patient.

4.6 Fertility, pregnancy and lactation

Pregnancy:
No clinical data are available for the use of allergen immunotherapy in pregnant women.
No animal studies were conducted to investigate reproductive toxicity.
The risk of occurrence of systemic reaction could not be excluded, either during initial phase or maintenance phase.
In any case, allergen immunotherapy should not be initiated during pregnancy.
A closed medical evaluation should assess the relevance of the continuation of the treatment during pregnancy.

Breast-feeding:
It is not known whether Alustal is excreted in human breast milk
No animal study was conducted to investigate the excretion of Alustal into milk.
A risk to the newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue Alustal therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility:
No fertility study was conducted with freeze dried extracts included in Alustal.

4.7 Effects on ability to drive and use machines

Alustal has no known influence on ability to drive and use machines.

4.8 Undesirable effects

During treatment with Alustal, patients are exposed to allergens that may cause injection site reactions and/or systemic allergic symptoms.

As with any allergen immunotherapy, allergic reactions including anaphylactic reactions (i.e; acute onset of an illness with involvement of the skin, mucosal tissue, or both, respiratory compromise, persistent gastrointestinal symptoms, or reduced blood pressure and/or associated symptoms) have been reported. Cases of anaphylactic shock with sudden circulatory collapse requiring rapid administration of adrenaline/epinephrine can occur. Inform patients of the associated signs and symptoms and have them seek immediate care and discontinue therapy should these occur. Treatment should only be resumed at the instruction of a physician.
Tolerance of a given dose in a patient may vary over time depending on specific reactivity of the individual and the environment.
Pre-treatment with anti-allergic agents (for example antihistamines) may reduce frequency and severity of adverse reaction.

Cases of delayed « serum sickness-like syndrome » including arthralgia, myalgia, urticaria, nausea, adenopathy and fever can occur. Inform patients of the associated signs and symptoms and discontinue therapy should these occur.

Concomitant administration of allergy symptomatic drugs (such as antihistamines) may be used to improve the tolerance of allergen immunotherapy.

The following table of adverse reactions is based on data from sollicitated reporting in 369 patients enrolled in clinical studies with frequencies as follows:
Very common (≥ 1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1,000 to <1/100)

System Organ Class	**Frequency**	**Adverse Reactions**
Immune system disorders	Common	Anaphylactic reaction
Nervous system disorders	Common	Headache
	Uncommon	Dizziness; Paresthesia
Eye disorders	Common	Conjunctivitis
Ear and labyrinth disorders	Uncommon	Ear pain
Cardiac disorders	Uncommon	Palpitations; Decreased blood pressure
Vascular disorders	Uncommon	Hot flush
Respiratory, thoracic and mediastinal disorders	Very common	Rhinitis
	Common	Asthma; Cough; Dyspnea, Bronchospasm
	Uncommon	Throat irritation, Laryngitis, Pharyngolaryngeal pain, Sinusitis, Bronchitis
Gastrointestinal disorders	Uncommon	Tongue oedema; Dysphagia; Abdominal pain; Nausea; Diarrhoea
Skin and subcutaneous tissue disorders	Common	Urticaria; Pruritus; Eczema; Erythema
	Uncommon	Face oedema

General disorders and administration site conditions	Common	Injection site oedema; Injection site pruritus; Injection site inflammation
	Uncommon	Injection site pain; Injection site erythema; Injection site nodule, Peripheral edema; Asthenia; Chest discomfort

Generally, injection site reactions do not imply modification of the therapeutic scheme.

Additionally cases of angioedema, laryngeal edema, wheezing, vomiting, malaise, injection site granuloma, generalized erythema, arthralgia, myalgia, serum sickness-like syndrome, lymphadenopathy, pyrexia and anaphylactic shock have been spontaneously reported during post marketing experience with unknown frequencies.

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:
Bulgaria
BDA
8, Damian Gruev
1303 Sofia Phone.: +359 2 8903417
web: www.bda.bg

4.9 Overdose
In case of injection of a dose higher than those prescribed, the risk and severity of adverse reaction may be increased, leading to systemic reactions or severe local allergic reactions.
Patient should be kept under medical supervision upon assessment of patient's condition.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Allergen extracts
ATC code: V01AA

The precise mechanism of action of allergens administered during the course of AIT is not clearly understood.
Treatment with AIT has shown to induce changes in T-lymphocyte responses, followed by elevations in allergen-specific IgG4,and/or IgG1 and sometimes IgA and decrease of specific IgE, A second and probably later immunologic response is immune deviation with a shift in the allergen specific T cell response.

5.2 Pharmacokinetic properties
No pharmacokinetic data are available in animals or in humans.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and genotoxicity.
Chronic administration of high dose levels of mite extracts contained in Alustal showed no signs of toxicity in rats by subcutaneous route. Genotoxicity studies were conducted with numerous extracts contained in Alustal and showed no mutagenic, aneugenic or clastogenic potential.

6. Pharmaceutical particulars

6.1 List of excipients
(in one vial of 5 ml suspension for injection):
Mannitol
Aluminium hydroxide
Sodium chloride
Phenol
Water for injection

6.2 Incompatibilities
None

6.3 Shelf life
18 months
Shelf life after opening of the container: 6 months (storage from +2ºC to +8˚C).

6.4 Special precautions for storage:
Alustal should be stored in a refrigerator from +2ºC to +8˚C.
Do not freeze.
Keep out of the reach and sight of children.
Shake before use.

6.5 Nature and contents of container:

Immediate packaging
Each vial contains 5 ml of suspension for injection:
The suspension for injection is packed in 12 ml vials of white glass type I, closed with a stopper of penicillin type and sealed with an aluminium cap with different colours, depending on the concentration:
Grey cap: 0.01 IR/ml or 0.01 IC/ml
Yellow cap: 0.1 IR/ml or 0.1 IC/ml
Green cap: 1 IR/ml or 1 IC/ml
Blue cap: 10 IR/ml or 10 IC/ml

Outer packaging: Polypropylene box.

Initial treatment: A box of 4 vials with increasing concentrations (0.01, 0.1, 1 and 10 IR/ml or IC/ml).

Maintenance treatment: A box of 1 vial with 10 IR/ml or IC/ml concentration.

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

7. Marketing authorization holder:
STALLERGENES
6 Rue Alexis de Tocqueville
92160 ANTONY
FRANCE

8. Marketing authorisation number
20060648

9. Date of first authorization / renewal of authorisation
15.11.2006 / 04.06.2012

10. Date of revision of the text: 01/2017

Appendix I List of allergen extracts applying for renewal

POLLENS		
Individual allergen products		
Weeds	**Grasses**	**Trees**
Extracts in IR/ml : *Ambrosia artemisiifolia* (Ragweed) *Artemisia vulgaris* (Mugwort) *Parietaria officinalis* (Erect wall pellitory) *Salsola kali* (Russian thistle) Wall pellitory (Parietaria judaica) Extracts in IC/ml : *Amaranthus retroflexus* (Rough pigweed) *Chenopodium album* (Fat hen) *Brassica napus* (Rape) *Humulus lupulus* (Hop) *Medicago sativa* (Alfalfa) *Chrysanthemum leucanthemum* (Ox-eye daisy) *Brassica nigra* (Mustard) *Urtica dioica* (Nettle) *Rumex acetosa* (Sorrel) *Taraxacum officinale* (Dandelion) *Plantago lanceolata* (Plantain) *Solidago Canadensis* (Golden rod) *Helianthus annuus* (Sunflower) *Trifolium pratense* (Red clover)	Extracts in IR/ml : *Cynodon dactylon* (Bermuda Grass) *Dactylis glomerata* (Cocksfoot) *Anthoxanthum odoratum* (Sweet vernal-grass) *Lolium perenne* (Rye-grass) *Poa pratensis* (Meadow grass) *Phleum pratense* (Timothy) *Secale cereale* (Rye) Extracts in IC/ml : *Agrostis capillari* (Bent grass) *Festuca pratensis* (Meadow fescue) *Holcus lanatus* (Yorkshire fog) *Avena sativa* (Oat) *Triticum aestivum* (Wheat) *Zea mays* (Maize) *Hordeum vulgare* (Barley) Wheat flour Couch grass	Extracts in IR/ml : *Alnus glutinosa* (Alder) *Betula pendula* (Birch) *Carpinus betulus* (Hornbeam) *Juniperus ashei* (Cupressaceae) *Corylus avellana* (Hazel) *Olea europaea* (Olive) Extracts in IC/ml : *Castanea sativa* (Chestnut) *Quercus robur* (Oak) *Cupressus sempervirens* (Cypress) *Acer pseudoplatanus* (Maple) *Fraxinus excelsior* (Ash) *Juniperus communis* (Juniper) *Fagus sylvatica* (Beech) *Aesculus hippocastanum* (Horse Chestnut) *Acacia baileyana* (Mimosa) *Morus alba* (Mulberry white) *Juglans regia* (Walnut) *Ulmus campestris* (Elm) *Populus alba* (Poplar) *Pinus sylvestris* (Pine) *Platanus acerifolia* (Plane) *Robinia pseudoacacia* (False acacia) *Salix caprea* (Willow) *Sambucus nigra* (Elder) *Tilia cordata (*Lime) *Ligustrum vulgare* (Privet)

POLLENS		
Mixture of allergens		
Weeds	**Grasses**	**Trees**
Extracts in IC/ml : ⁂ Compositae: - *Chrysanthemum leucanthemum* (Ox-eye daisy) - *Xanthium strumarium* (Cockelebur) - *Taraxacum officinale* (Dandelion) - *Solidago Canadensis* (Golden rod) In equal parts ⁂ Chenopodiaceae : - *Chenopodium album* (Fat hen) - *Amaranthus retroflexus* (Rough pigweed) In equal parts ⁂ Weed mixtures: - *Medicago sativa* (Alfalfa) - *Trifolium pratense* (Red clover) - *Brassica nigra* (Mustard) - *Urtica dioica* (Nettle) - *Rumex acetosa* (Sorrel) In equal parts	Extracts in IR/ml : ⁂ 3 grasses : - *Dactylis glomerata* (Cocksfoot) - *Lolium perenne (*Rye-grass) - *Phleum pratense* (Timothy) ⁂ 5 grasses : - *Dactylis glomerata* (Cocksfoot) - *Anthoxanthum odoratum* (Sweet vernal-grass) - *Lolium perenne* (Rye-Grass) - *Poa pratensis* (Meadow grass) - *Phleum pratense* (Timothy) ⁂ 12 grasses: - *Agrostis capillaris* (Bent grass) - *Arrhenatherum elatius (*Oat grass) - *Avena fatua* (Wild oat) - *Bromus inermi* (Bromus) - *Cynodon dactylonn* (Bermuda Grass) - *Dactylis glomerata* (Cocksfoot) - *Festuca pratensis* (Meadow fescue) - *Anthoxanthum odoratum* (Sweet vernal-grass) - *Holcus lanatus* (Yorkshire fog) - *Lolium perenne* (Rye-Grass) - *Poa pratensis* (Meadow grass) - *Phleum pratense* (Timothy) Extracts in IC/ml : ⁂ 4 cereals : - *Avena sativa* (Oat) - *Triticum aestivum* (Wheat) - *Zea mays* (Maize) - *Hordeum vulgare* (Barley)	Extracts in IR/ml : ⁂ Betulaceae : - *Alnus glutinosa* (Alder) - *Betula pendula* (Birch) - *Carpinus betulus* (Hornbeam) - *Corylus avellana* (Hazel) Extracts in IC/ml : ⁂ Fagaceae : - *Castanea sativa* (Chesnut) - *Quercus robur* (Oak) - *Fagus sylvatica* (Beech) ⁂ Oleaceae : - *Olea europaea* (Olive) - *Fraxinus excelsior* (Ash) - *Ligustrum vulgare* (Privet) In equal parts ⁂ Salicaceae : - *Populus alba* (Poplar) - *Salix caprea* (Willow) In equal parts ⁂ Trees' mixture : - *Acer pseudoplatanus* (Maple) - *Aesculus hippocastanum* (Horse Chestnut) - *Platanus acerifolia* (Plane) - *Robinia pseudoacacia* (False acacia) - *Tilia cordata (*Lime) In equal parts

MITES	
Individual allergens	**Mixture of allergens**
Extracts in IR/ml : *Dermatophagoides pteronyssinus* *Dermatophagoides farinae* *Blomia tropicalis* Extracts in IC/ml : *Acarus siro* *Glyciphagus domesticus* *Lepidoglyphus destructor* *Tyrophagus putrescentiae* *Pyroglyphus africanus*	Extracts in IR/ml : ⁂ House dust mites : - *Dermatophagoides pteronyssinus* - *Dermatophagoides farinae* Extracts in IC/ml : ⁂ Storage mites : - *Acarus siro* - *Glyciphagus domesticus* - *Lepidoglyphus destructor* - *Tyrophagus putrescentiae* In equal parts

MOULDS	
Individual allergens	**Mixtures of allergens**
Extracts in IC/ml : Moulds : *Alternaria alternata* *Botrytis cinerea* *Chaetomium globosum* *Epicoccum purpurascens* *Fusarium solani* *Helminthosporium halodes* *Merulius lacrymans* *Mucor racemosus* *Pullularia pullulans* *Rhizopus nigricans* *Stemphyllium botryosum* *Trichothecium roseum* Yeasts and Dermatophytes: Epidermophyton flocosum Tricophyton rubrum	Extracts in IC/ml : ⁂ *Saccharomyces* mix : - *Saccharomyces cerevisiae* - *Saccharomyces minor* ⁂ *Ustilago* mix : - *Ustilago avenae* - *Ustilago tritici* - *Ustilago holci* - *Ustilago zeae* ⁂ *Aspergillus* mix : - *Aspergillus fumigatus* - *Aspergillus niger* - *Aspergillus nidulans* ⁂ *Cladosporium* mix : - *Cladosporium cladosporioides* - *Cladosporium herbarum* ⁂ *Penicillium* mix : - *Penicillium digitatum* - *Penicillium expansum* - *Penicillium notatum*

ALLERGENS OF ANIMAL ORIGIN AND INSECTS	
Individual allergens	**Mixtures of allergens**
Extracts in IR/ml : Epithelia : Cat Extracts in IC/ml : Epithelia : Horse Guinea pig Hamster Rabbit Dog Insects : German cockroach (*Blatella germanica*) Corn moth (*Ephestia kuehniella*) Mosquito (*Aedes communis*)	Extracts in IC/ml : ⁎ Feather mixture - Duck - Goose - Hen