SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nasovac-S
Influenza Vaccine (Human, Live attenuated) Freeze Dried 2012 Formula.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each freeze dried vaccine vial is reconstituted with the entire contents of diluent - Sterile water For Inhalation, USP that is supplied along with the vaccine, using the supplied syringe and needle-free device.

Each vial of 1 dose (0.5 mL) contains:

Component	Quantity/dose (EID_{50}/dose)	Specifications	Active/ Non-active	Reason for inclusion
A/17/California/09/38 (H1N1)*	$\geq 10^7$	In-house	Active	Immunizing agent
A/17/Perth/09/87 (H3N2)*	$\geq 10^7$	In-house	Active	Immunizing agent
B/56/Brisbane/60/08*	$\geq 10^{6.5}$	In-house	Active	Immunizing agent
Partially hydrolysed gelatin	2.5%	IP/BP/PhEur/ InHouse	Non-active	GS stabilizer (stabilizer I)
Sorbitol	5.0%	IP/BP/PhEur	Non-active	GS stabilizer (stabilizer I)
L-Alanine	0.1%	BP/PhEur	Non-active	Stabilizer II
L-Histidine	0.21%	BP/PhEur	Non-active	Stabilizer II
Tricine	0.3%	In House	Non-active	Stabilizer II
L-Arginine hydrocloride	1.6%	BP/PhEur	Non-active	Stabilizer II
Lactalbumin hydrolysate	0.35%	In House	Non-active	Stabilizer II
Phosphate buffered saline	Base	---	Non-active	Base

*Propagated in embryonated hens eggs
The three strains are antigenically similar to the strains recommended by the World Health Organization (WHO) for the 2011 and 2012 Southern hemisphere.

3. PHARMACEUTICAL FORM

NASOVAC-S is lyophilized vaccine for reconstitution with the diluent-Sterile Water For Inhalation provided by the manufacturer. White friable mass freely soluble in diluent. After reconstitution with the entire content of the supplied container of diluent, the vaccine is a homogeneous suspension.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the active immunization for the prevention of influenza disease caused by two influenza A subtype viruses and one influenza Type B virus which are expected to circulate in the 2012 season. The vaccine should be used in accordance with official guidance.

4.2. Posology and method of administration

Each freeze dried vaccine vial is reconstituted using the entire contents of sterile water for inhalation that is supplied along with the vaccine, using the supplied syringe and plastic draw up needle.
A dose of 0.5 ml is administered as 0.25 ml per nostril using a 1.0 ml syringe and a intranasal spray device. The sprayer device creates a fine spray that primarily deposits the vaccine in the nose and nasopharynx. A single intranasal dose is recommended for people above 2 years of age.
The diluent supplied is specially designed for use with the vaccine. Only this diluent must be used to reconstitute the vaccine. Do not use diluents from other types of vaccine or from other manufacturers. Using an incorrect diluent may result in damage to the vaccine and/or serious reactions to those receiving the vaccine. Diluent must not be frozen, but should be kept cool.
The diluent and reconstituted vaccine should be inspected visually for any foreign particulate matter and / or variation of physical aspects prior to administration. In the event of either being observed, discard the diluent or reconstituted vaccine.

4.3. Contraindications

4.3.1 Hypersensitivity

Nasovac-S is contraindicated in individuals with a history of hypersensitivity, especially anaphylactic reactions to eggs, egg proteins, gelatin, lactalbumin or other vaccine components.

4.3.2 Concomitant Pediatric and Adolescent Aspirin Therapy and Reye's syndrome

Nasovac-S is contraindicated in children and adolescents (2-17 years of age) receiving aspirin therapy or aspirin-containing therapy, because of the association of Reye's syndrome with aspirin and wild-type influenza infection.

4.4. Special warnings and special precautions for use

Nasovac-S should under no circumstances be injected.

As with all vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Nasovac-S should not be administered to any individuals with active wheezing.

If the individual has a history of Guillain-Barré syndrome the decision to give Nasovac-S should be based on careful consideration of the potential benefits and potential risks.

Immunization should be postponed in patients with severe febrile illness or acute infection. The vaccine can be given to people with minor illnesses (e.g., diarrhea or mild upper respiratory tract infection without fever). However, if nasal congestion is present that might limit delivery of the vaccine to the nasal lining, then delaying of vaccination until the nasal congestion is reduced should be considered.

People already suffering from cold, cough, fever, bodyache or other flu-like symptoms should be clinically evaluated and if necessary, appropriate treatment should be given. In such cases, Nasovac-S vaccination should be postponed at least till recovery.

Administration of Nasovac-S, to immune-compromised persons should be based on careful consideration of potential benefits and risks. There is no clinical data available on the use of this vaccine in immune-compromised persons. Antibody response in such patients may be insufficient.

The safety of Nasovac-S in individuals with underlying medical conditions that may predispose them to complications following wild-type influenza infection has not been established. The decision to give Nasovac-S should be based on careful consideration of the potential benefits and potential risks.

4.5. Interactions with other medicinal products and other forms of interaction

Do not administer Nasovac-S to children or adolescents who are receiving aspirin therapy or aspirin-containing therapy [see Contraindications (4.3.2)].

The concurrent use of Nasovac-S with antiviral agents that are active against influenza A and/or B viruses has not been evaluated. However, based upon the potential for antiviral agents to reduce the effectiveness of Nasovac-S, do not administer this vaccine until 48 hours after the cessation of antiviral therapy. Antiviral agents should not be administered until two weeks after administration of this vaccine unless medically indicated. If antiviral agents and Nasovac-S are administered concomitantly, revaccination should be considered when appropriate.

There are no data on co-administration of Nasovac-S with other vaccines. However, if co-administration with another vaccine is indicated, immunisation may be carried. It should be noted that the adverse reactions may be intensified.

There are no data regarding co-administration of Nasovac-S with other intranasal preparations.

The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

4.6. Pregnancy and lactation

A developmental and reproductive toxicity study has been performed in female rats administered Live attenuated pandemic H1N1 vaccine either once, twice or thrice (during the period of organogenesis), at approximately 2 human dose equivalents per occasion, by intranasal instillation and has revealed no evidence of maternal toxicity, fetotoxicity or teratogenicity. There are

however, no studies in pregnant women. Because animal studies are not always predictive of human response, Nasovac-S should be administered during pregnancy only if clearly needed.

It is not known whether Nasovac-S is excreted in human milk. Therefore, as some viruses are excreted in human milk and additionally, because of the possibility of shedding of vaccine virus and the close proximity of a nursing infant and mother, caution should be exercised if Nasovac-S is administered to nursing mothers.

4.7. Effects on ability to drive and use machines

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

4.8. Undesirable effects

No fatality or SAE was reported in the Phase I and Phase II/III studies. None of the subjects experienced any hypersensitivity reaction. There was no effect on vital functions. No case of new onset chronic medical conditions like Guillain-Barré Syndrome was reported.
Formulation A (with similar composition as stated above) was compared with Formulation B (with lower titres of all 3 virus strains).
A total of 41 occurrences of solicited local reactions were reported in Group I subjects, and 34 in Group II subjects. Solicited local reactions reported by subjects included nasal discomfort (4.3% Vs 1.8%), sneezing (6.1 % Vs 6.0%), stuffy nose (3 % in both groups), runny nose (4.3% Vs 4%), loss of smell (1.8% Vs 1.2%), red eyes (3% in both groups), lacrimation (2.4 % Vs 1.8%), and facial swelling (0 % Vs 06%).

A total of 30 occurrences of solicited systemic reactions were reported in Group I and 33 in Group II subjects. Solicited systemic reactions reported by subjects included headache (7.3% Vs 8.4%), chills (0.6% Vs 1.2%), fatigue (2.4% Vs 1.8%), sore throat (2.4% Vs 1.2%), cough (1.8% Vs 3.6%), myalgia (1.2% Vs 0.6%), arthralgia (0.6 Vs 0.6%,) irritability (0.6% Vs 0.0%), wheezing (0.6% Vs 1.2%), loss of appetite (0.0% Vs 1.2%), and nausea (0.6% Vs 0.0%).

Most of the solicited local and systemic reactions were of Grade 1 (mild) severity and none were Grade 3 (severe). All of them resolved without sequelae within 1-8 days. Most of them didn't require concomitant medications.

There were few unsolicited event reported in both the groups. In the study, 13 unsolicited adverse events were reported. All except one, AEs were Grade 1 (mild) in severity and none of the AE was reported as Grade 3 (severe). Only one AE (coryza) in Group I, and 2 AEs (cough and fever) in Group II were deemed to be caused by study vaccine.

4.9. Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Nasovac-S is a live trivalent vaccine for administration by intranasal spray. It contains three vaccine virus strains of A/H1N1, A/H3N2 & Type B influenza virus cultivated on embryonated hen eggs. The three strains are antigenically similar to the strains recommended by the World Health Organization (WHO) for the 2012 Southern hemisphere.
The influenza virus strains in the vaccine are (a) cold-adapted (ca) (i.e., it replicates efficiently at 25°C, a temperature that is restrictive for replication of many wild-type influenza viruses); (b) temperature-sensitive (ts) (i.e., it is restricted in replication at 39°C, a temperature at which many wild-type influenza viruses grow efficiently); and (c) attenuated (att) (it does not produce classic influenza-like illness in the ferret model of human influenza infection). The cumulative effect of the antigenic properties and the ca, ts, and att phenotypes is that the attenuated vaccine virus replicates in the nasopharynx to induce protective immunity.

Immune mechanisms conferring protection against influenza following receipt of live attenuated influenza vaccines are not fully understood, though it is well-established that these vaccines provide clinical protection to the majority of the vaccinees. Serum antibodies, mucosal antibodies, and influenza-specific T cells may play a role in prevention and recovery from infection. NASOVAC-S contains live attenuated influenza viruses that must infect and replicate in cells lining the nasopharynx of the recipient to induce immunity. Vaccine viruses capable of infection and replication can be cultured from nasal secretions obtained from vaccine recipients (shedding)

The immune response of the vaccine is in the line with the reported results of other seasonal or pandemic live attenuated Influenza vaccines.

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

Efficacy study of NASOVAC-S in naïve ferrets (which is an established model of influenza) using homologous influenza viruses as challenge was conducted. Viral load, viral shedding and pathological analysis showed reduced levels of all three parameters in vaccinated animals after challenge irrespective of the challenge virus clearly demonstrating high efficacy of NASOVAC-S for all three strains.
Nasovac-S has undergone Single-dose and Repeated-dose toxicity studies in mice and rats when administered intranasally. In single-dose studies, vaccine was given at a dose of 0.1 ml/animal (equal to one human dose in absolute terms) and they were observed for 14 days for toxic effects. No vaccine-related untoward effects were found in animals receiving Nasovac-S.
In repeated-dose toxicity studies, three doses of 0.1 ml/animal (equal to one human dose in absolute terms) were given intranasally to animals on day 0, 7 and 14 and were subsequently sacrificed. Necropsy was done to assess adverse effects on any organs. No vaccine-related adverse effects were found in the study animals receiving Nasovac-S.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Nasovac-S contains the following excipients:

Component	Concentration	Specifications
Partially hydrolysed gelatin	2.5%	IP/BP/PhEur/ InHouse
Sorbitol	5.0%	IP/BP/PhEur
L-Alanine	0.1%	BP/PhEur
L-Histidine	0.21%	BP/PhEur
Tricine	0.3%	In House
L-Arginine hydrocloride	1.6%	BP/PhEur
Lactalbumin hydrolysate	0.35%	In House
Phosphate buffered saline	Base	---

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. Shelf-life

Shelf life for the vaccine will be 9 months.

6.4. Special precautions for storage

NASOVAC-S must be transported and stored between 2° to 8°C. The vials should not be frozen.

6.5. Nature and contents of the container

NASOVAC-S is filled and lyophilized in 13 mm USP Type 1 clear tubular glass vials of 16.5 mm diameter and 40 mm height and 5.0 mL overflow volume. Vials are stoppered with a 13 mm Grey butyl Rubber 'Lyo' stopper and sealed with 13 mm orange coloured plastic flip top aluminum seal.

6.6. Special precautions for disposal

The vaccine should be allowed to reach room temperature before use.

Once Nasovac-S, Intranasal has been administered, the sprayer should be disposed of according to

the standard procedures for medical waste (e.g., sharps container or biohazard container).

7. MARKETING AUTHORIZATION

Serum Institute of India Ltd,

212/2, Hadapsar, Pune-411028

India.

8. MARKETING AUTHORIZATION NUMBER (S)

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9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

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