Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Preflucel suspension for injection in a pre-filled syringe
Influenza Vaccine (split virion, inactivated, prepared in cell cultures)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza virus (inactivated, split) of the following strains*:

A/California/07/2009 (H1N1)	15 micrograms HA**
A/Victoria/361/2011 (A/H3N2)	15 micrograms HA**
B/Hubei-Wujiagang/158/2009 (B)	15 micrograms HA**
	per 0.5 ml dose

* propagated in Vero cells (continuous cell line of mammalian origin)
** haemagglutinin

This vaccine complies with the WHO recommendation (Northern Hemisphere) and EU decision for the 2012/2013 season.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection in a pre-filled syringe. PREFLUCEL is a clear to opalescent suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylaxis of influenza in adults and elderly.
The use of PREFLUCEL should be based on official recommendations.

4.2 Posology and method of administration

Posology
Adults (18 years of age and older) and elderly (older than 60 years of age): 0.5 ml

Paediatric population
The safety and efficacy in subjects below 18 years of age have not been evaluated (see section 5.1).

Method of administration
Immunization should be carried out by intramuscular injection (into the deltoid muscle).
For instructions of the vaccine before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.) or residues (e.g. formaldehyde, benzonase or sucrose).

It is recommended to postpone the immunization in patients with moderate or severe acute illness with or without fever.

4.4 Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine. Anaphylaxis has been reported with PREFLUCEL.

PREFLUCEL should under no circumstances be administered intravascularly.

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient. As with other intramuscular injections, PREFLUCEL should be given with caution in individuals with bleeding disorders such as hemophilia or on anticoagulant therapy, to avoid the risk of hematoma following the injection.

This medicinal product contains less than 1 mmol sodium (23 mg) per 0.5 ml, i.e. essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interaction

PREFLUCEL may be given at the same time as other vaccines. Do not mix with any other vaccine in the same syringe or vial.

Immunization should be carried out on separate limbs. It should be noted that adverse reactions may be intensified. The immunological response may be diminished if the patient is undergoing immunosuppressant treatment. Although not seen with PREFLUCEL, following influenza vaccination, false positive results in serology tests using the ELISA method to detect antibodies against HIV1, Hepatitis C and especially HTLV1 have been observed. The Western Blot technique disproves the false-positive ELISA test results. The transient false positive reactions could be due to the IgM response to the vaccine.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of PREFLUCEL in pregnancy and lactation has not been assessed in clinical trials. In general, data from influenza vaccinations in pregnant women do not indicate adverse fetal and maternal outcomes attributable to the vaccine. The use of this vaccine may be considered from the second trimester of pregnancy. Physicians are advised to carefully consider the potential risks and benefits for each specific patient before prescribing PREFLUCEL. For pregnant women with medical conditions that increase their risk of complications from influenza, the vaccine may be administered according to national recommendations.

Breastfeeding

PREFLUCEL may be used during lactation.

Fertility

The effects of PREFLUCEL vaccine on male fertility have not been established.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Safety data regarding use of PREFLUCEL are based on data from clinical studies in more than 10,000 adult and elderly subjects (8,600 adults aged 18-59 years; 2,225 elderly aged 60+ years). The most common adverse reactions observed

in clinical studies were headache, myalgia, injection site pain, fatigue and malaise. PREFLUCEL has not been studied in a paediatric population.

List of adverse reactions

Adverse reaction frequencies are reported as:
Very common (≥1/10)
Common (≥ 1/100, <1/10)
Uncommon (≥1/1000, <1/100)
Rare (≥ 1/10000, <1/1000)

Organ class	**Very common ≥1/10**	**Common ≥1/100, <1/10**	**Uncommon ≥1/1000, <1/100**	**Rare ≥1/10000 <1/1000**
Immune system disorders				Hypersensitivity Anaphylactic Reaction
Nervous system disorders	Headache*		Sensory disturbance* (hypoaesthesia, hyperaesthesia, paraesthesia)	Dysgeusia
Eye disorders			Ocular Hyperemia, Eye irritation, Eye discharge	
Respiratory, thoracic and mediastinal disorders		Cough Oropharyngeal pain Rhinorrhoea	Throat irritation, Pharyngeal oedema, Dyspnea	
Gastrointestinal disorders		Nausea* Vomiting*	Abdominal pain	Dysphagia*
Skin and subcutaneous tissue disorders		Hyperhidrosis	Pruritus, Erythema	Urticaria
Investigations		Blood pressure increased		
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia*	Musculoskeletal stiffness	
General disorders and administration site conditions	Injection site reaction: Pain* Systemic reactions: Fatigue, Malaise	Injection site reaction: Swelling Erythema Induration* Systemic reactions: Chills, Pyrexia	Injection site reaction: Pruritus, Hemorrhage, Warmth* Systemic reactions: Chest Discomfort	Oedema peripheral
Vascular disorders				Syncope

* These reactions usually disappear within 1-2 days without treatment.

One case of multiple sclerosis was reported in a single male subject. First symptoms occurred 6 weeks after vaccination. The causal relationship to vaccination cannot be ruled out.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Overdosage is unlikely to have any untoward effect.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, purified antigen, ATC code: J07BB02
Seroprotection is generally obtained within 2 to 3 weeks. The duration of post-vaccinal immunity to homologous strains or to strains closely related to the vaccine strains varies but is usually 6 to 12 months.

Clinical efficacy
Clinical efficacy of the vaccine against influenza infection has been investigated during the 2008/2009 season in the pivotal phase 3, randomized, placebo-controlled, double-blind study conducted in healthy subjects 18 to 49 years of age, receiving PREFLUCEL (N=3626) or placebo (N=3620). Efficacy of PREFLUCEL was defined by the prevention of culture confirmed influenza infection (CCII) for matching and mismatching strains.

Vaccine Efficacy Estimates During Influenza Season 2008/2009§		
Influenza Strains	Matching Strains§§	Matching and Mismatching Strains together§§§
	Adults 18-49 years of age N=3626	Adults 18-49 years of age N=3626
A/H1N1 (95% CI)	79.0% (59.7 to 89.0)	75.2% (55.4 to 86.2)
A/H3N2 (95% CI)	50.0%[1] (-173.0 to 90.8)	50.0% (-173.0 to 90.8)
A Strains Together (95% CI)	77.0% (57.9 to 87.4)	73.5% (54.0 to 84.7)
B Strain (95% CI)	100%[2] (4.1 to 100.0)	60.1%[3] (9.5 to 82.4)
ALL Strains (95% CI)	78.5% (60.8 to 88.2)	71.5% (54.7 to 82.1)

§ Phase 3 clinical study conducted in the US during Influenza season 2008/2009
§§ Efficacy against influenza strains antigenically similar to the vaccine strains (confirmed by viral culture)
§§§ Efficacy against influenza strains irrespective of antigenic match (confirmed by viral culture and/or RT-PCR)
[1] 2 documented cases of CCII in vaccine group and 4 documented cases in placebo group
[2] 4 documented cases of CCII, all in placebo group
[3] 28 influenza B strains were isolated, of which, 4 represented a lineage level match to the vaccine strain (Yamagata lineage).

Vaccine efficacy calculated for all strains, irrespective of antigenic match was consistent throughout the study with a mean, cumulative efficacy per week of 68% - 83%, over the entire influenza season.

Immunogenicity
In the pivotal phase 3 study in adults aged 18-49 years (2008/2009) the immune responses to each of the antigens are shown in the table below:

PREFLUCEL			
Strain specific anti-HA			

antibody	A/H1N1	A/H3N2	B
	Adults 18-49 years of age N=3473	Adults 18-49 years of age N=3473	Adults 18-49 years of age N=3473
Seroprotection rate* (95% CI)	88.0% (86.8 to 89.0)	93.3% (92.4 to 94.1)	97.1% (96.5 to 97.7)
Seroconversion rate ** (95% CI)	70.4% (68.9 to 71.9)	79.1% (77.7 to 80.4)	65.7% (64.1 to 67.3)
Geometric mean fold increase*** (95% CI)	11.1 (10.52 to 11.74)	13.5 (12.85 to 14.20)	7.6 (7.22 to 7.97)

* Seroprotection = HI Titer ≥ 40
** Seroconversion = negative pre-vaccine HI titer and post-vaccination HI titer ≥ 40: Significant increase = positive pre-vaccination HI titer and at least a 4-fold increase in post-vaccination HI titer
*** Geometric mean fold increase is the increase of antibody response (hemaglutination inhibition titer) after vaccination compared with prior to vaccination. The increase of antibody response is reported as geometric mean of fold increase of antibody titer in each individual subject 21 days after vaccination compared with the titer prior to vaccination.

In a previous randomized, placebo-controlled, double-blind, phase 3 clinical study conducted in healthy subjects 18 to 49 years of age during the 2007/2008 season, 1744 subjects received PREFLUCEL. Seroprotection rates across all three influenza strains ranged from 75.9% to 97.1%, seroconversion rates from 57.0% to 71.7%, and geometric mean fold increase 21 days after vaccination from 6.5 to 10.8 over baseline HI titers.

A randomized, double-blind, active-controlled, phase 3 study evaluated the immunogenicity and safety of PREFLUCEL in adults and elderly subjects (50 years of age and older) during the 2008/2009 season, receiving PREFLUCEL (N = 2842) or a comparator egg-derived trivalent influenza virus vaccine (N = 366). Seroprotection rate, seroconversion rate and the geometric mean fold increase (GMFI) are shown in the table below:

PREFLUCEL					
Strain specific anti-HA antibody	A/H1N1		A/H3N2		B	
	50-59 years of age N=1248	60+ years of age N=1548	50-59 years of age N=1248	60+ years of age N=1548	50-59 years of age N=1248	60+ years of age N=1548
Seroprotection rate* (95% CI)	76.9% (74.5; 79.2)	71.1% (68.7; 73.3)	90.1% (88.3; 91.7)	90.8% (89.3; 92.2)	87.5% (85.5; 89.3)	82.8% (80.8; 84.6)
Seroconversion rate** (95% CI)	50.6% (47.7; 53.4)	37.2 % (34.8; 39.7)	70.1% (67.5; 72.6)	59.8% (57.3; 62.3)	49.1% (46.3; 51.9)	37.5% (35.0; 39.9)
Geometric mean fold increase*** (95% CI)	5.18 (4.78;5.63)	3.35 (3.14;3.57)	9.67 (8.86;10.55)	6.14 (5.71; 6.59)	4.59 (4.25;4.97)	3.20 (3.00; 3.40)

* Seroprotection = HI Titer ≥ 40; CHMP criterion >70% for subjects 18-59 years of age and >60% for subjects aged 60 years and older
** Seroconversion = negative pre-vaccine HI titer and post-vaccination HI titer ≥ 40: Significant increase = positive pre-vaccination HI titer and at least a 4-fold increase in post-vaccination HI titer; CHMP criterion >40% for subjects 18-59 years of age and >30% for subjects aged 60 years and older
*** Geometric mean fold increase is the increase of antibody response (hemagglutination inhibition titer) after vaccination compared with prior to vaccination. The increase of antibody response is reported as geometric mean of fold increase of antibody titer in each individual subject 21 days after vaccination compared with the titer prior to

vaccination; CHMP criterion >2.5 for subjects 18-59 years of age and >2.0 for subjects aged 60 years and older

The egg-derived active comparator achieved seroprotection rates across all three influenza strains ranging from 86.7% to 95.8% and 79.7% to 96.2%, in subjects aged 50-59 years (N=143) and aged 60 years and older (N=212), respectively. At 21 days after vaccination seroconversion rates were 61.5% to 87.4% (subjects aged 50-59 years) and 47.6% to 72.6% (subjects aged 60 years and older). Geometric mean fold increase 21 days after vaccination ranged between 5.8 and 13.9, 4.0 and 10.7, respectively in both age strata.
PREFLUCEL has not been studied in a paediatric population and therefore, data on immune response are not available for this age group (see section 4.2).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional toxicity studies. PREFLUCEL was well tolerated and immunogenic in mice, rats and guinea pigs. In single and repeat- dose toxicity studies in rats there was no evidence of systematic toxicity and the vaccine was locally well tolerated. Genotoxicity and carcinogenic potential were not assessed because these studies are not appropriate for a vaccine. There were no adverse reactions following maternal vaccination in developmental and reproductive studies in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol
Sodium chloride
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

1 year

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep in the outer carton in order to protect from light.

6.5 Nature and contents of container

1 or 10 prefilled syringes (type I glass) with a latex-free plunger stopper (bromobutyl rubber) with attached needle;

1 or 10 prefilled syringes (type I glass) with a latex-free plunger stopper (bromobutyl rubber) without attached needle.

Each syringe contains 0.5 ml suspension. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use.
Shake the pre-filled syringes well prior to administration so that the vaccine suspension is thoroughly mixed. After shaking, PREFLUCEL is a clear to opalescent suspension. The vaccine should be inspected visually for any foreign particulate matter and/or variation in physical appearance prior to administration. In the event of either being observed, discard the vaccine.
Remove needle guard as follows:

1. Hold the pre-filled syringe at the lower part of the needle guard fixed onto the glass recipient (Fig. 1).
2. Use the other hand to take the upper part of the needle guard between thumb and forefinger, and twist to break the seal (tamper evident) (Fig. 2).
3. Remove the detached part of the needle guard from the needle by a **vertical** movement (Fig.3).

Following removal of the needle guard, PREFLUCEL should be used immediately.

To avoid loss of sterility and/or clogging of the needle, it should not be left without protection for prolonged periods of time. Therefore, the needle guard should only be removed after shaking and immediately prior to use.

Additional information for PREFLUCEL syringe without attached needle:

After removing the syringe cap, attach the needle immediately and remove the needle shield prior to administration. Once the needle is attached, the vaccine must be administered immediately.

To minimize the risk of local adverse reactions care must be taken to avoid droplets of vaccine on the tip or the external surface of the needle prior to injection. If alcohol is used at the injection site, it should be allowed to dry completely before vaccination, and should not come in contact with the vaccine.

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

7 MARKETING AUTHORISATION HOLDER

Nanotherapeutics Bohumil S.R.O.,
Bohumil 138,
28163 Jevany,
Czech Republic

8 MARKETING AUTHORISATION NUMBER

PA2077/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th June 2011

Date of last renewal: 20th September 2015

10 DATE OF REVISION OF THE TEXT

January 2016