SUMMARY OF PRODUCT CHARACTERISTIC

1. **Name of the Medicinal Product:**

   Name: PANAF-Premium / Combipack of Snake Venom Antiserum With Sterile Water For Injection (Pan Africa)**.**

   Strength: After reconstitution, each ml of Polyvalent Snake Venom Antiserum (Pan Africa) neutralizes at a minimum:–

   Bitis arietans ≥ 25 LD_{50}

   Bitis gabonica ≥ 25 LD_{50}

   Bitis nasicornis ≥ 20 LD_{50}

   Bitis rhinoceros ≥ 25 LD_{50}

   Echis leucogaster ≥ 25 LD_{50}

   Echis ocellatus ≥ 25 LD_{50}

   Echis Carinatus ≥ 25 LD_{50}

   Naja haje ≥ 25 LD_{50}

   Naja melanoleuca ≥ 20 LD_{50}

   Naja nigricollis ≥ 20 LD_{50}

   Dendroaspis polylepis ≥ 25 LD_{50}

   Dendroaspis viridis ≥ 25 LD_{50}

   Dendroaspis jamesoni ≥ 25 LD_{50}

   Dendroaspis angusticeps ≥ 25 LD_{50}

   Apart from above there is additional para specific venom neutralization of following snake species: *Echis pyramidum, Echis romani, Naja annulifera, Naja guineenesis, Naja mossambica, Naja nigricincta, Naja pallida, Naja peroescobari, Naja savannula, Naja senegalensis and Naja subfulva.*

2. **Quality and Quantitative Composition**

   Qualitative Declaration: Snake venom antiserum (Pan Africa) is a sterile containing enzyme refined anti snake equine immunoglobulin $F(ab')_2$ fragments.

   i. Glycine B.P. : Stabilizer

   ii. Sodium Chloride B.P.: Excipient (Isotonic)

   iii. Cresol B.P. : Preservative

3. Pharmaceutical Form:

Lyophilized powder for solution for injection.

Freeze dried product, white or slightly yellow powder or solid friable masses. After reconstitution colourless to very faintly yellow liquid, free from turbidity**.**

4. Clinical Particulars

4.1 Therapeutic Indications:

PANAF−Premium™ is indicated for bites caused by several species of African snakes in line with WHO recommendations, including Bitis arietans, Bitis gabonica, Bitis nasicornis, Bitis rhinoceros, Echis leucogaster, Echis ocellatus, Echis pyramidum, Echis romani, Dendroaspis angusticeps, Dendroaspis jamesoni, Dendroaspis polylepis, Dendroaspis viridis, Naja annulifera, Naja guineenesis, Naja haje, Naja melanoleuca, Naja mossambica, Naja nigricollis, Naja nigricincta, Naja pallida, Naja peroescobari Naja savannula, Naja senegalensis and Naja subfulva, where the patients present with visible clinical signs and symptoms of envenoming:−

Systemic Envenomation:

(i) Neurotoxic envenoming- Moderate or no local swelling, progressive descending paralysis with ptosis and paralysis of eye movements.

Earlier symptoms of neurotoxicity include blurred vision/double vision, feeling of heaviness of eyelids and apparent drowsiness, difficulty raising the eyebrows and puckering the forehead even before ptosis. High risk of respiratory failure is suggested by poor mouth opening and limited tongue protrusion, dysarthria, dysphagia, dyspnoea, distress, restlessness, sweating, respiratory muscle weakness and impaired. Consciousness as a result of respiratory paralysis or airway obstruction and/or circulatory failure

(ii) Non-Neurotoxic envenoming- (Haemorrhagic & Cytotoxic envenoming) Painful and progressive swelling with blood−stained tissue fluid leaking from bite wound and spontaneous systemic bleeding from gums (gingival sulci), coagulopathy defected by 20 min WBCT with or without external bleeding, persistent bleeding from fang marks, nausea, vomiting and shock. Hypovolemic shock, blistering and bruising severe pain at bite site and

throughout affected limb and painful tender enlargement of local lymph glands and irreversible tissue death (necrosis/gangrene).

(iii) Spitting cobra ophthalmia− Venom spat into the eyes should be washed out as soon as possible using copious amounts of water or other bland fluids (e.g., milk) Local anaesthetic eye drops may need to be applied once only if eyes are being held shut due to pain, after which a protective eye pad dressing should be applied. Topical antibiotics should be applied as for corneal injuries. Antivenom is not indicated

4.2 Posology and Method of Administration:

PANAF−Premium™ is supplied in 20ml glass vial with 10m sterilized Water for Injection BP as diluent. Withdraw diluent is 10ml sterile syringe and insert needle through vial stopper and inject into the vial. Mix the contents gently by swirling action and avoid vigorous shaking. Serum should be used as soon as possible after reconstitution.

Currently, Snake antivenom is the only specific antidote for snake envenoming and prompt administration of an adequate dose of antivenom is of paramount importance for neutralization of unbound circulating snake venom components for early response to treatment Antivenom is most effective when given intravenously. Any delay in administration may result in increased dose requirement and decreased effectiveness

Snake antivenom is effective in preventing or reversing many of the harmful effects of snakebite envenoming. When administered early antivenoms are not just lifesaving, but can prevent some irreversible effects such as local tissue damage (necrosis, gangrene) so sparing patients some of the suffering caused by snake venom, and allowing faster recovery, less time in hospital and a more rapid transition back to a productive life.

Snake antivenom should be administered intravenously and not by other routes, it can be given by intravenous infusion after dilution 1:1 in isotonic fluid over 30−60 minutes, or by intravenous injection at a rate of about 5ml per minute after dilution 1:1 in isotonic fluid. Total volume of antivenom and diluent administered should not exceed 500 ml/hr. It giving more than 25 vials, the dose should be diluted 1:1 with isotonic fluid and administered over 90−120 minutes**,**

Children should receive the same dose of antivenom as adults, but it is imperative to avoid fluid overload.

Correct identification of the biting snake is usually very difficult or impossible unless a dead snake is brought with the patient or an adequate photograph of the actual snake for expert assessment. There may be variability in clinical signs and symptoms due to many factors such as size of victim, comorbidities, body part bitten, activity after bite, individual sensitivity to venom components, bite characteristics (bite number, depth interposition of clothing, amount of venom injected, condition of fangs, duration of snake's dinging to the victim and chewing), biting snake species, nature of first aid given, and time to antivenom administration after bits. As the clinical signs vary due to many factors, a syndromic approach (supported by epidemiological data about prevalence of snake species prevalent in that region) is recommended for initiating appropriate clinical management.

Initial Doses:

Dose recommendations below are based on the recognition of the variable composition of snake venoms leading to differences in potency within and between species. They also recognize the wide variation in the amount of venom that may be injected by individual specimens, particularly by large cobras (Naja) and mambas (Dendroaspis). These dose recommendations may be updated as new data based on clinical practice or clinical trials experience becomes available, and subject to review and approval by WHO.

Species Group	Genus	Recommended Initial Dose
African adders	Bitis	3–6 vials
African carpet vipers	Echis	1–3 vials
African mambas	Dendroaspis	10–25 vials
African cobras	Naja	20–40 vials

1) **Non-Neurotoxic Envenoming Syndrome-** The clinical syndrome of envenoming is dominated by haemorrhagic, cytotoxic or procoagulant effects by African adders/vipers (Bitis spp.), or carpet vipers (Echis spp.) and African spitting cobras (e.g. Naja nigricollis, N. pallida, N. ashei, N, mossambica, etc.) The amount of injected venom can vary greatly from

one species to another. For carpet vipers it is generally less than 20 mg, but African adders and spiting cobras commonly inject >300 mg of venom. Considering worst case scenario, the following doses are recommended for each species−

For bites by carpet vipers (Echis spp.)− It is recommended to administer initial dose of 1−3 vials.

For bites by African adders (Bitis spp.)− It is recommended to administer initial close of 3−6 vials

For bites by African spitting cobras (Naja spp.)- It is recommended to administer initial dose of 20−40 vials.

2) **Neurotoxic Envenoming Syndrome-** The clinical syndrome of envenoming is dominated by neurotoxic effects potentially causing rapid death through paralysis of airway and breathing muscles and is caused by neurotoxic species of cobra (e.g. Naja haje, N. senegalensis, N melanoleuca, etc.) or mamba (Dendroaspis polylepis, D. viridis, D. angusticeps and D. jamesoni), Neurotoxic cobras can inject >300 mg venom and mambas may inject >100 mg venom. Considering worst case scenario, the following doses are recommended for each species−

   For bites by mambas (Dendroaspis spp.)- It is recommended to administer initial dose of 10−25 vials.

   For bites by neurotoxic cobras (Naja spp.)− It is recommended to administer initial dose of 20−40 vials.

Administration of repeat doses should be based on the clinical picture post−antivenom and decided by the treating clinician. For non−neurotoxic snake bites progression of local or systemic signs of envenoming more than 6 hours post−antivenom indicates need for additional antivenom. In particular, continued spontaneous bleeding or positive 20 minutes WBCT at 6 hours after presumed Echis spp. or Bitis spp. envenoming indicates need for repeat dosing. For neurotoxic snake bites any worsening of paralysis (particularly related to airway and breathing) more than 1 hour post−antivenom indicates need for additional antivenom.

Supportive Treatment:

Antivenom alone cannot be relied upon to reverse neurotoxicity or prevent its progression to respiratory paralysis. It is essential that close attention be given to protecting and maintaining airway and breathing. Basic airway management and assisted breathing is lifesaving. Appropriate interventions such as Guedel airways, laryngeal mask airways, supplementary oxygen, bag–mask ventilation and if available endotracheal intubation and initiation of mechanical ventilation should be implemented as soon as indicated. For bites by neurotoxic cobras the use of anticholinesterase drugs like Neostigmine can temporarily reverse paralysis, but these drugs are not safe or appropriate for treatment of mamba bites. When used for cobra bites the co–administration of atropine is essential to block potentially serious muscarinic effects, such as bradycardia, bronchospasm, and an increase in secretions. Two anticholinergic drugs are available for this purpose, namely, atropine and glycopyrrolate. Atropine or glycopyrrolate may be used as anticholinergic agents.

In non–neurotoxic syndrome, recovery of normal haemostatic function may be accelerated by giving fresh whole blood, fresh frozen plasma, cryoprecipitate, or platelet concentrates but only after administration of an effective dose of antivenom. Acute kidney injury is uncommon after snakebites in Africa but may be a complication of prolonged hypotension (shock) or sepsis. Ideally, urine output should be monitored closely from time of presentation and if urine output falls below 1.5 mg/kg/hr in 24 hours, then appropriate renal therapy should be instituted. Cautious rehydration with isotonic fluids can be attempted but diuretics such as furosemide and mannitol are not recommended. If these measures fail, dialysis may be indicated.

Massive local swelling (e.g., after bites by large Bitis spp.) may cause hypovolemic shock (fall in blood pressure, especially orthostatic) from fluid extravasation. Fluid replacement is essential, commonly after puff adder (B. arietans) envenoming. Other measures include pain management (most of the bite sites are painful requiring administration of pain killers such as paracetamol) and surgical intervention if required. In addition to above, routine administration of tetanus toxoid is recommended. Antibiotics are indicated if the wound is already necrotic, has been

tampered with or when signs of infection appear. Expert surgical advice should be sought where debridement of necrotic tissue in needed. Rapidly−evolving secondary bacterial necrotizing fasciitis is a dangerous complication requiring urgent parenteral antibiotics and surgical debridement.

Immediate Actions and First Aid:

Quick and positive measures should be taken to meet the emergency. Do not try to catch or kill the snake. Avoid further contact with the snake by the victim and bystanders. The patient should not be allowed to walk or run but should be carried by stretcher and kept as still as possible, ideally in the (left−lateral) recovery position. Reassure the patient to address anxiety and fear. Immobilizing the bitten limb with a splint and firm (but not tight) bandages is appropriate. Ligatures and tight tourniquets should be avoided. A pressure pad applied firmly over the bite site may be beneficial without exposing the patient to risk of local ischemia. Small sips s of water may be given but eating and drinking should be avoided due to risk of vomiting and aspiration of vomitus into the airway in neurotoxic snakebites. Patient should be taken to the nearest medical facility without delay.

4.3 Contraindications:

There are no known contraindications for the administration of Snake Venom Antiserum (Pan Africa).

4.4 Special Warnings and Precautions for use:

Proper precautions are necessary when dealing with patients with known hypersensitivity to constituents of the product Premedication with inj. Adrenaline (250 mcg 1:1000 for adults 100−200 mcg 1.1000 for children) has been shown to reduce the risk of severe early adverse reactions to equine immunoglobulin−based antivenoms in a clinical trial in hemotoxic bites, intramuscular injections should be avoided until coagulopathy has been corrected to avoid formation of haematoma and oozing of blood. Tight (arterial) tourniquets are contraindicated after snake bite because of their well−established risk of causing gangrene of the affected limb.

4.5 Interaction with other medicinal products and forms of other interactions:

There no drug interactions reported.

4.6 Pregnancy and Lactation:

However, considering the risk associated with snake bite envenoming, pregnancy is not a contraindication to the administration of PANAF−Premium subsequent to snake bites.

4.7 Effects on ability to drive and use machine:

Usually patients requiring PANAF−Premium are hospitalized in critical condition and not in a position to drive or operate machine

4.8 Undesirable Effects:

Combipack of Snake Venom Antiserum with Sterile Water for Injection (Pan Africa) being derived from equines is heterologous to humans and hence can give occasional reactions.

Before injection of Snake Venom Antiserum (Pan Africa), it is necessary to enquire from the patient,

1) Whether he/she has received injections of horse serum previously.

2) Whether there is personal or family history of allergy, i.e., asthma, eczema or drug allergy.

Every care should be taken to prevent reactions which could be countered immediately by injection of 1 ml. of 1:1000 adrenalines which should be always kept handy, before injecting the dose of Snake Venom Antiserum (Pan Africa). In allergic individuals, the Snake Venom Antiserum (Pan Africa) 1 ml of Adrenaline 1:1000 may be injected intramuscularly at the same time as the antiserum. In some cases symptoms such as itching, urticarial rash, pain in joints and muscles, fever, enlargement of lymph glands, appear about 7−12, days after injection of serum. These should be treated with antihistamines and corticosteroids. Usually these symptoms of serum sickness last a few days and patients recover without any complications. There can be transient tenderness at injection site and a brief rise in body temperature which does not require treatment.

Adverse Reactions:

PANAF−Premium™ derived from equines, is heterologous to humans and can give either early or late reactions. Inj. Adrenaline should be always kept handy, before starting the doses of Snake Venom Antiserum.

Antivenom Reactions			
Type	**Early (Within few hours)**		**Late 5 days or more**
	Anaphylactic	**Pyrogenic**	**Serum Sickness**
Timeline	Develops within 3 − 60 minutes of starting anti−antivenom.	Develops within 1−2 hours of starting antivenom.	Appear after about 5−24 (Avg.7) days after injection of antivenom.
Symptoms	Cough, tachycardia, itching (especially of scalp) urticaria, fever, nausea, vomiting and headache	Chills, fever, vasodilatation and fall of blood pressure	Itching, urticaria, fever, arthralgia, Peri−articular swelling, proteinuria, and sometimes neurological symptoms.
Recommended Treatment	1. Stop administration of antivenom temporarily. 2. Give inj. Adrenaline (1:1000) 0.5 to 1 ml for adults and 0.01 mg/kg for children by I.M. route. 3. Repeat the dose if required every 5 to 10 minutes. 4. In addition, administration of 10−25 mg of chlorpheniramine maleate for adults / 0.2mg/kg for children may be given by I.V. route followed by Hydrocortisone 100 mg for adults / 2 mg/kg for children by I.V. route. 5. In pyrogenic reaction patient may be physically cooled (tepid sponging of the skin and fanning and given antipyretics (paracetamol). 6. Hypovolaemia should be corrected by I.V. fluids.		Serum sickness should be treated 5−day course of anti−H1 histamines such as chlorphenamine. Patients who failed to respond in 24−48 hours should be given 5− day course of once daily prednisolone. Chlorphenamine dose: Adults 2 mg 6 hourly, children 0.25 mg/kg/day in divided doses. Prednisolone dose: Adults 20mg, children 0.7 mg/kg/day as a single daily dose.

4.9 Overdose:

No health hazards are anticipated.

5. Pharmacological Properties:

5.1 Pharmacodynamic Data: Not performed.

Pharmacotherapeutic Group: Antivenom (Antisera).

ATC Code: J06AA03

Bioavailability− Bioequivalence BA−BE study is Not Applicable. The product is injectable preparation. Injectable product intended to be administered via the intravenous route. The advantage is bypassing the "Hepatic first−pass system" and direct absorption in the bloodstream.

5.2 Pharmacokinetic Data: Not performed.

Bioavailability− Bioequivalence BA−BE study is Not Applicable. The product is injectable preparation. Injectable product intended to be administered via the intravenous route. The advantage is bypassing the "Hepatic first−pass system" and direct absorption in the bloodstream.

5.3 Preclinical Safety Data: Performed.

Non−clinical evaluation is done by carrying out acute intravenous toxicity studies on two animal species i.e. One rodent (mouse) and one non−rodent (rabbit).

The quantitative measures of acute intravenous toxicity of Snake Venom Antiserum (Pan Africa), viz. the median lethal dose (LD_{50}), the minimum lethal dose (MLD) and the maximum tolerated dose (MTD) could not be determined. However, based on the findings of this study, the values of above measures of Snake Venom Antiserum (Pan Africa) in mouse were found to be greater than 20 ml/kg body weight (which is 0.5 to 2 times of its human equivalent dose (HED) in mouse, and 6 to 24 times of its clinical dose).

6. Pharmaceutical Particulars:

6.1 List of Excipients:

i. Glycine B.P. : Stabilizer

ii. Sodium Chloride B.P. : Excipient (Isotonic)

iii. Cresol B.P. : Preservative

6.2 Incompatibilities: None.

6.3 Shelf life:

− Shelf life of the medicinal product as packages for sale: 48 Months.

− Shelf life after dilution or reconstitution according to directions: Immediate use.

− Shelf−life after first opening the container: Immediate use.

6.4 Special precautions for storage: Store below 30˚C and Dark Place.

6.5 Nature and contents of container (and Special equipment for use, administration or implantation):

A clear USP type I glass vial, closed with a 20mm Grey Bromobutyl rubber closure and a 20 mm royal blue flip−off aluminium seal and

10 ml Sterilised Water for Injections BP ampoule for reconstitution, is a clear, colorless, sterile solution filled in 10 ml LDPE Plastic Ampoule.

Administration: Withdraw diluent is 10ml sterile syringe and insert needle through vial stopper and inject into the vial. Mix the contents gently by swirling action and avoid vigorous shaking. Serum should be used as soon as possible after reconstitution.

Pack Size: 1 glass vial having 10ml of lyophilized powder and 1 ampoule of sterile water for Injection 10 ml per carton.

6.6 Special Precautions for disposal and other handling:

Snake Venom Antiserum (Pan Africa) solution for injection is obtained by reconstitute with 10 ml water for injection ampoule.

The reconstituted solution is for single use only.

Preparation:

1. Withdraw diluent in 10ml a syringe from the 10 ml SWFI ampoule.
2. Insert the needle through vial stopper and inject in to vial.
3. Mix the content gently by swirling action and avoid vigorous shaking.
4. Serum should be used as soon as possible after reconstitution.
5. Snake antivenom should be administered intravenously and not by other routes, it can be given by intravenous infusion after dilution 1:1 in isotonic fluid over 30−60 minutes, or by intravenous injection at a rate of about 5ml per minute after dilution 1:1 in isotonic fluid. Total volume of antivenom and diluent administered should not exceed 500 ml/hr. It giving

more than 25 vials, the dose should be diluted 1:1 with isotonic fluid and administered over 90−120 minutes.

7. **Marketing Authorization Holder:**

   Premium Serums and Vaccines Pvt. Ltd.

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