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Proceeding Paper

A Clinical Review of a Polyvalent F(ab')$_2$ Antivenom (Inoserp^{TM} PAN-AFRICA) in the Management of Snakebite Envenomation in Sub-Saharan Africa: Clinical Studies and Actual Use since Its Introduction in 2012 †

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Abstract: Inoserp^{TM} PAN-AFRICA is a polyvalent F(ab')$_2$ antivenom that has been specifically developed for the management of snakebite envenomation in sub-Saharan Africa. The antivenom provides a very large coverage of medically important species in sub-Saharan Africa, with at least 24 species covered. This review presents all clinical data available on the use of Inoserp^{TM} PAN-AFRICA in sub-Saharan Africa since it was introduced in 2012. The antivenom has been used in more than 20 countries from west to east Africa, with approximately 200,000 vials distributed through marketing approvals, special import permits, and organizations such as armies or NGOs. Four clinical studies have been performed in five countries of West and Central Africa, encompassing 22 clinical sites and involving 676 patients exposed to Inoserp^{TM} PAN-AFRICA. Patients were rather young, with a median age ranging from 18 to 38 years, and a great majority were males, with a sex ratio (M/F) ranging from 2.7 to 4.5, according to the study. Snakebite envenomation was representative of the sub-Saharan African region with mostly hemorrhagic and cytotoxic but also neurotoxic syndromes. Overall, patients received an average dose of two to three vials, which was enough to obtain a rapid control of symptoms in the great majority of cases. The observed lethality rate was 0% to 4.4%, depending on the study. Adverse events were mostly of mild or moderate intensity and have been reported in 5 to 11% of patients. Other available data, such as published reports of patient cases, as well as the most updated pharmacovigilance surveillance report in 2022, have been used to complete this review. Overall, Inoserp^{TM} PAN-AFRICA benefits from a large experience in sub-Saharan Africa. Clinical data available consistently show a very good efficacy and safety profile of the antivenom.

Keywords: snakebite; envenomation; antivenom; Africa; clinical; review

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1. Introduction and Background

1.1. Objective of This Review

Snakebite envenomation (SBE) is a serious health issue mostly affecting poor populations in tropical regions. In sub-Saharan Africa, the number of SBE cases was estimated to be over 300,000, leading to more than 7000 deaths and up to 14,000 victims with disabilities each year [1]. Antivenoms are the only specific treatment of SBE. However, there is a lack of information and fear of using antivenoms among healthcare providers in sub-Saharan Africa. Indeed, the reputation of antivenoms has been damaged by the safety risk associated with the use of the first generation and the uncertain quality and specificity of some antivenoms still available in sub-Saharan Africa. In the past decades, the development of new antivenoms has benefited from the major advances in applied biochemistry and immunology. This was successfully achieved with the design of Inoserp^{TM} PAN-AFRICA, a polyvalent antivenom covering most of the medically important snake

species of sub-Saharan Africa. The objective of this review is to provide the most comprehensive profile of the clinical efficacy and safety of Inoserp^{TM} PAN-AFRICA to healthcare providers, researchers, decision makers, and any people involved in SBE management in sub-Saharan Africa.

1.2. Use of Inoserp^{TM} PAN-AFRICA in Sub-Saharan Africa

Since 2012, Inoserp^{TM} PAN-AFRICA has been used in more than 20 countries from west to east Africa, as detailed in Table 1 hereafter. Over 200,000 vials of Inoserp^{TM} PAN-AFRICA have been distributed mainly through marketing approval special import permits but also through organizations such as armies or NGOs.

Table 1. Geographic distribution of the use of Inoserp^{TM} PAN-AFRICA.

West Africa: Benin, Burkina Faso, Ghana, Guinea, Ivory Coast, Mali, Niger, Senegal, Sierra Leone, Togo	
Central Africa: Cameroon, Central African Republic, Chad, Equatorial Guinea, Gabon, Republic of Congo	
East Africa: Djibouti, Kenya, Sudan, Tanzania, Uganda	
Southern Africa: Angola, Zambia	

Other *polyspecific* antivenoms currently available in sub-Saharan Africa include ASNA-C (Bharat Serums and Vaccines, India), ASNA-D (Bharat Serums and Vaccines, India), FAV-A (MicroPharm Ltd, UK), ET-Plus (Instituto Clodomiro Picado, Costa Rica), Antivip-A (Instituto Bioclon, Mexico), Premium-A (Premium Serums and Vaccines, India), Premium-CA (Premium Serums and Vaccines, India), African-Ten (Premium Serums and Vaccinesn India), SAIMR Polyvalent (South African Vaccine Producers, South Africa), Afriven 10 (VINS Bioproducts, India), Echiven Plus (VINS Bioproducts, India), VINS-CA (VINS Bioproducts, India), Central Africa-6 (Biological E Limited, India) and Pan Africa – 10 (Biological E Limited, India).

1.3. Specificities of Inoserp^{TM} PAN-AFRICA

Inoserp^{TM} PAN-AFRICA is composed of equine origin F(ab')$_2$ immunoglobulin fragments. Following the hyperimmunization phase, immunoglobulins raised against the different venom components are collected and digested by enzymes into F(ab')$_2$ fragments. As recommended by WHO guidelines [2], F(ab')$_2$ present several advantages: In contrast to complete IgG, F(ab')$_2$ have a better safety profile as they do not contain Fc fragments known to trigger side effects. F(ab')$_2$ also benefit from a better pharmacokinetic profile than Fab fragments that are eliminated very quickly in the body. One of the major characteristics of Inoserp^{TM} PAN-AFRICA is that it is highly purified thanks to a specific manufacturing process developed by Inosan Biopharma. Following a series of fractionation and filtration processes, the level of F(ab')$_2$ reaches over 95% of the composition of the antivenom [3]. In addition, the manufacturing process is performed in perfectly closed conditions, with sterility and microbiology controls carried out regularly throughout the entire manufacturing process. Therefore, antivenoms manufactured by Inosan Biopharma meet viral safety requirements, do not contain pyrogen agents, and are preservative-free. Another key feature of Inoserp^{TM} PAN-AFRICA is that it contains highly specific F(ab')$_2$. This means

that there is a high proportion of effective F(ab')$_2$ capable of specifically binding to the toxic components of the venoms and neutralizing them. Therefore, Inoserp^{TM} PAN-AFRICA can neutralize more venom with fewer proteins [3]. This high-yield production process enables the inclusion of antibodies of additional species in the same vial for a broader coverage. In fact, Inoserp^{TM} PAN-AFRICA is polyvalent and covers all species that are medically important (WHO category 1) in sub-Saharan Africa [4], as detailed in Table 2 hereafter. Finally, Inoserp^{TM} PAN-AFRICA is lyophilized, which makes its transport and storage easy and inexpensive as it is not cold-chain dependent, which is a decisive asset in tropical regions such as in sub-Saharan Africa.

Table 2. Main characteristics of Inoserp^{TM} PAN-AFRICA.

IgG Type	F(ab')$_2$ (Equine)
F(ab')^2	Over 95%
Protein	Less than 10%
Preservatives	None
Species coverage	**Viperidae:** *Cerastes cerastes*, *Echis ocellatus*, *Echis leucogaster*, *Echis pyramidum*, *Bitis arietans*, *Bitis rhinoceros*, *Bitis nasicornis*, *Bitis gabonica* **Elapidae:** *Dendroaspis polylepis*, *Dendroaspis viridis*, *Dendroaspis angusticeps*, *Dendroaspis jamesoni*, *Naja anchieta*, *Naja annulifera*, *Naja ashei*, *Naja nigricollis*, *Naja haje*, *Naja katiensis*, *Naja melanoleuca*, *Naja mossambica*, *Naja nubiae*, *Naja pallida* and *Naja senegalensis* **Atractaspididae:** *Atractaspis irregularis* **Colubridae:** *Dispolidus typus*
Formulation	Lyophilized
Storage	Up to 30 °C with possible excursions up to 40 °C for a reduced period

2. Methodology

This review presents all clinical data available on the use of Inoserp^{TM} PAN-AFRICA in sub-Saharan Africa since it was introduced in 2012. The main source of data comes from the clinical studies that have been performed and published but also from all other available sources, such as published reports of patient cases and the most updated pharmacovigilance surveillance report. Four clinical studies have been performed in 5 countries of West and Central Africa, encompassing 22 clinical sites and involving 676 patients, as summarized in Table 3 and detailed below.

Table 3. Characteristics of clinical studies involving Inoserp^{TM} PAN-AFRICA.

Study Reference	Design	Countries	Number of Clinical Sites	Nb of Patients Treated
Chippaux et al., 2015 [5]	Multicenter prospective clinical study	Benin Guinea	3	209
Coulibaly et al., 2018 [6]	Monocenter prospective observational study	Mali	1	154
Lam et al., 2019 [7]	Multicenter prospective cohort study	Senegal	4	63
Chippaux et al., 2022 [8]	Multicenter prospective clinical study	Cameroon	14	250
Overall statistics on clinical studies		5 countries	22 clinical sites	676 patients

- Evaluation of a new polyvalent antivenom against snakebite envenomation (Inoserp^{TM} PAN-AFRICA) in two different epidemiological settings—Northern Benin and Mar-

itime Guinea (Chippaux et al., 2015) [5]: This is the first clinical study performed with 209 patients treated overall. The study objective was to evaluate the clinical efficacy and safety of Inoserp^{TM} PAN-AFRICA in 2 countries with different SBE profiles: North Benin, where Echis ocellatus represents 75% of envenomation, and Maritime Guinea, which is well known for a high incidence of elapids bites (Naja and Dendroaspis gender).

- Antivenom serotherapy in Mali: experience at Kati reference health center, Kouligoro region (Coulibaly et al., 2018) [6]: This single-center observational study was performed on 154 patients in a health center in west Mali with the objective of assessing the clinical efficacy and safety of Inoserp^{TM} PAN-AFRICA in a region with high incidence of *Echis ocellatus* bites.
- Evaluation of the efficacy and tolerance of Inoserp^{TM} PAN-AFRICA in Senegal (Lam et al., 2019) [7]: This cohort multicenter study was performed on 63 patients in Senegal. The objective was to evaluate the safety and efficacy of Inoserp^{TM} PAN-AFRICA under realistic conditions at rural health facilities experiencing cytotoxic, hemotoxic, and neurotoxic envenomation.
- Snakebites in Cameroon: evaluation of snake antivenom in Africa (ESAA) and real-life conditions (Chippaux et al., 2022) [8]: This is the largest multicenter clinical study performed with Inoserp^{TM} PAN-AFRICA. Overall, 250 patients have been treated in 14 clinical sites in Cameroon. The main objective was to study the short- and mid-term safety and efficacy profile of the antivenom in real conditions.

In addition, several publications reporting the use of Inoserp^{TM} PAN-AFRICA in patients have been identified: 1 patient presenting with neurotoxic envenomation in Guinea [9], 1 patient bitten by a carpet viper (*Echis ocellatus*) in Togo [10], and 1 herpetologist bitten by a puff adder (*Bitis arietans*) in Guinea [11].

Finally, Inosan Biopharma maintains pharmacovigilance surveillance of the use of Inoserp^{TM} PAN-AFRICA worldwide and compiles an updated Periodic Safety Update Report (PSUR) each year. The last PSUR used for the review is dated 28 February 2022 and encompasses reports received from 2013 to December 2021.

3. Results

3.1. Clinical Studies

3.1.1. Demographic Characteristics and SBE Syndromes

In most cases, the patients included were young male adults with a median age of 18 years in Benin to 38 years in Mali and a sex ratio (M/F) of 2.7 in Senegal to 4.5 in Benin. Most patients presented with hemorrhagic syndrome (up to 93% in Cameroon); however, two studies reported more than 10% of neurotoxic syndromes (Guinea and Senegal). *Echis ocellatus* was the species involved in most hemorrhagic syndrome cases. However, when it was feasible, other species were identified, such as *Bitis arietans* (Cameroon), *Naja melanoleuca* (Cameroon), *Dendroaspsis viridis* (Guinea), *Dendroaspsis polylepis* (Guinea), *Dendroaspsis jamesoni* (Cameroon), and *Atractaspis species* (Cameroon). The severity of envenomation varied from mild (grade 1) to serious (grade 4) according to the ASV severity score [12]. Patients could present rather quickly (4 h 50 of median time in Cameroon) to slowly (24 h of median time in Benin or in Senegal hospitals) after a snake bite. See details in Table 4 hereafter.

Table 4. Demographic characteristics and SBE syndromes.

Study Reference	Country	Age Median (Q25%–Q75%)	Sex-Ratio (M/F)	SBE Syndromes % Hemorrhagic (Including Positive WBCT) [(1)]	SBE Syndromes % Neurotoxic	Time from Snake Bite to Admission (Median)
Chippaux et al., 2015 [5]	Benin (n = 100)	18 (13–29)	4.5	90%	2%	24 h
	Guinea (n = 109)	30 (19–41)	3	88%	12%	6 h
Coulibaly et al., 2018 [6]	Mali (n = 154)	38 NA	3.7	82%	NA [(2)]	NA [(2)]
Lam et al., 2019 [7]	Senegal (n = 63)	22 (13–35)	2.7	38%	13%	6 h (Health Unit) 24 h (Hospital)
Chippaux et al., 2022 [8]	Cameroon (n = 250)	25 (14–50)	NA [(2)]	93% [(3)]	9% [(3)]	4 h 50

WBCT = Whole Blood Clotting Test; NA = Not Available. Some patients presented both hemorrhagic and neurotoxic syndromes.

3.1.2. Efficacy and Safety Profile

The mean number of vials administered was consistent from one study to another, ranging from 1.4 to 2 per patient, except in Cameroon, where patients received 3.2 vials on average. The length of hospitalization varied from 1.6 to 5.8 days on average but could largely be influenced by local practices. The global lethality rate was low (2.5%) and was often associated with delayed treatment or neurologic syndromes. Adverse events, mostly of mild or moderate intensity, were reported in 5 to 11% of patients. See details in Table 5 hereafter.

Table 5. Efficacy and safety profile.

Study Reference	Country	Number of Vials per Patient (Mean)	Length (Days) of Hospitalization (Mean)	Lethality	Adverse Events
Chippaux et al., 2015 [5]	Benin (n = 100)	1.8	5.8	3 (3%)	11 (11%)
	Guinea (n = 109)	1.4	4.5	1 (1%)	6 (5.5%)
Coulibaly et al., 2018 [6]	Mali (n = 154)	2	1 to 5 (Min–Max)	0 (0%)	14 (6.5%)
Lam et al., 2019 [7]	Senegal (n = 63)	1.4	1.6	2 (3.2%)	3 (4.8%)
Chippaux et al., 2022 [8]	Cameroon (n = 250)	3.2	NA	11 (4.4%)	NA

NA = Not Available.

3.2. Supporting Data

3.2.1. Published Patient Cases

Among the three patient cases published, there were two adult women (including one who was breastfeeding) and one man who was 64 years old. SBE involved three different species: *Dendroaspis gender*, *Echis ocellatus*, and *Bitis arietans*. In all cases, the antivenom was taken rather rapidly (less than 6 h), and four to six vials were administered depending on the case. All patients gradually improved without sequela. No side effects were reported.

3.2.2. Pharmacovigilance Surveillance

According to the spontaneous sources and the literature, 17 non-serious and 23 serious adverse events have been reported to Inosan Biopharma since 2012. These safety reports

are consistent with the safety profile specified in the approved product information. Based on all safety information available to date, Inoserp™ PAN-AFRICA has a positive risk–benefit profile.

4. Discussion

In a recent review of antivenoms available in sub-Saharan Africa [13], the authors conclude that there is a lack of good quality clinical data. This current review aims to fill this critical gap. According to this current review, Inoserp™ PAN-AFRICA is safe and effective in treating snakebite victims. However, some limitations are associated with this review: For feasibility reasons, the clinical studies reported were not designed as comparative randomized studies. Also, the proportion of elapid bites remains low in comparison to viper bites, reflecting the actual epidemiology in the region. Finally, the number of pharmacovigilance cases is clearly under-reported as this may not be part of the medical routine in many health centers in Africa.

5. Conclusions

This review summarizes all clinical data on Inoserp™ PAN-AFRICA after 10 years of use. With an estimated number of 200,000 vials distributed in over twenty countries and four prospective clinical studies performed in five countries, Inoserp™ PAN-AFRICA benefits from a large clinical experience in sub-Saharan Africa. All clinical information available consistently indicates that Inoserp™ PAN-AFRICA effectively controls envenomation symptoms and that it has an excellent safety profile.

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Conflicts of Interest: The author declares being an employee of Inosan Biopharma.

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