Abdala

PRODUCT WITH EMERGENCY USE AUTHORIZATION GRANTED BY THE CENTER FOR STATE CONTROL OF MEDICINES, EQUIPMENTS AND MEDICAL DEVICES (CECMED)

Authorized for Emergency Use: Resolution No. 113/21.
Date of issue: July 9, 2021.

Pediatric application extended use from 2 years old.
Date of issue: October 27, 2021.

CURRENT STATUS

Authorized for emergency use in Cuba, Venezuela, Vietnam and Nicaragua.

Authorization for the administration as a booster dose, starting 6 months after completing the immunization scheme against COVID-19 approved in Cuba.

Clinical trial phase 1-2 on COVID-19 convalescent patients (after phase 1):
https://rpcec.sld.cu/ensayos/RPCEC00000382-Sp.

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CHARACTERISTICS OF THE VACCINE

During the pandemic caused by the SARS-CoV-2 virus, most of the neutralizing antibodies and about 50% of the cellular response against this virus are directed to the spike protein (S), which contains the receptor-binding domain (RBD), the angiotensin-converting enzyme 2 (ACE2).

Abdala is a subunit vaccine, developed for vaccination against SARS-CoV-2 virus. As active pharmaceutical ingredient, it contains the receptor binding domain (RBD) and as inactive ingredients, phosphate salts and aluminum hydroxide gel adjuvant.

It is manufactured at the Center for Genetic Engineering and Biotechnology (CIGB, Havana, Cuba), with a production system of more than twenty years of experience, complying with the current good production practices and in accordance with the recommendations of the World Health Organization (WHO).

Abdala is administered intramuscularly three times in a short schedule, every 14 days (0-14-28 days). Currently, the vaccine has shown to be stable at 2 and 8 °C.

Abdala's production platform is based on *Pichia pastoris* yeast, which has been used in the Heberbiovac HB® preventive recombinant vaccine against the hepatitis B virus, registered in more than 30 countries and certified by the WHO.

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CLINICAL RESULTS

Abdala Clinical Study phase 1-2 in 792 volunteers generated a high level of seroconversion of anti-RBD antibodies in more than 90% of vaccinated individuals, between 19 to 80 years old, just 14 days after the last immunization. Also, the functionality of the induced antibodies was evidenced, with a positive correlation in assays for inhibition of binding to the SARS-CoV-2 virus receptor and in viral neutralization studies.

In phase 3 clinical study of vaccine efficacy in 48 290 volunteers (multicenter, randomized, double-blind, placebo-controlled), Abdala demonstrated 92.28% efficacy in reducing the risk of suffering from symptomatic COVID-19 disease.

The results of a clinical trial evaluating the immunogenicity of this vaccine applied with a 3-dose schedule between 12 and 18 years old, compared to those of a similar trial conducted with the same vaccine and schedule, in which its efficacy was demonstrated, in a population between 19 and 29 years old (immune bridge), similar results in all immunological variables were shown.

On July 9, 2021, the Cuban regulatory authority Center for the State Control of Medicines, Equipments and Medical Devices (CECMED) granted the Abdala's Emergency Use Authorization.

92.28 % efficacy rate against symptomatic COVID-19.

100 % efficacy rate at preventing the severe systemic disease.

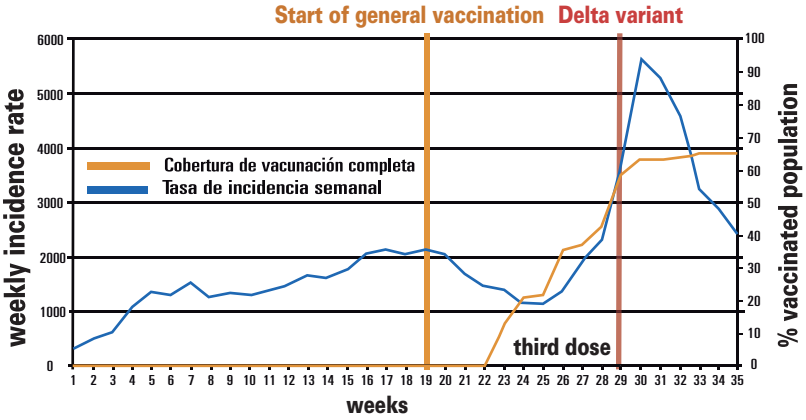
100 % efficacy rate at preventing death in immunized patients.

The efficacy of Abdala, evaluated in phase 3, was measured in a context where the Alpha and Beta strains of SARS-CoV-2 were circulating.

EFFECTIVENESS RESULTS

Abdala vaccine proved to be very effective, plus hygienic-sanitary measures, in reducing the incidence of COVID-19 in Havana, in a very complex scenario due to the predominance of the Delta variant of SARS-CoV-2 virus, one of the most contagious. The hygienic-sanitary measures indicated by the country's authorities and the vaccination with Abdala in Havana from July 11 to August 31, led to a reduction in the incidence of the infection, during the pandemic peak caused by the Delta variant of the virus.

Incidence and complete vaccination coverage, according to statistical weeks. Havana 2021



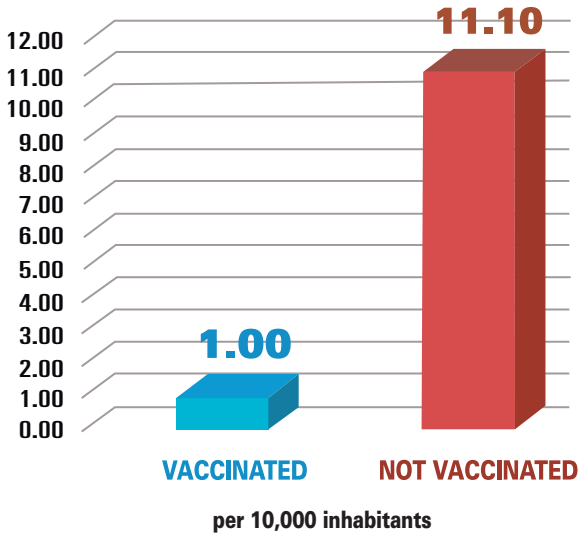
Effectiveness against serious form and death

The Abdala vaccine protects against the severe form of COVID-19 and death from this disease, in 92% and 90.7% respectively. Its effectiveness was demonstrated in a study in Havana from July 11 to August 31, 2021 in the complex entry scenario of the Delta variant of SARS-CoV-2.

TYPE OF EFFECTIVENESS	Severe/ Critical	Death
RR (IC 95%)	0,080 (0.065 - 0.116)	0,010 (0.079 - 0.149)
EFECTIVIDAD (IC 95%)	92,0 (88.4 - 93.5)	90.7 (85.1 - 92.1)

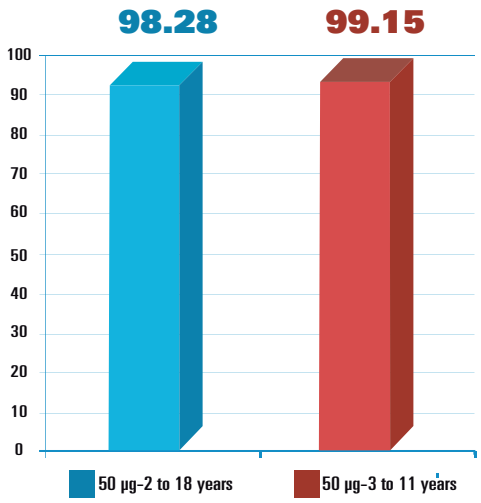
Severe case rate

Havana, June 11 - August 31, 2021



Of the people who became ill with COVID-19, those not vaccinated with Abdala in Havana were 11 times more prone to the severity of the disease than vaccinated people, demonstrating the high effectiveness of Abdala.

RESULTS IN PEDIATRIC CLINICAL TRIAL



Seroconversión: aumento de los títulos de anticuerpos IgG anti-RBD, cuatro veces o más a partir del inicio de la vacunación.

The Abdala vaccine showed high levels of seroconversion after vaccination in the age strata studied, between 3 and 18 years during the Ismaelillo pediatric clinical study.

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ADVANTAGES

- Abdala is a subunit protein vaccine, therefore there is no risk of pathogenicity, toxicity is very low and safety very high.
- The production system for the vaccine is robust.
- It is a potential vaccine that can protect against mutant strains from the use of booster doses without causing reactogenicity.
- The RBD antigen, designed by researchers at the CIGB, has peculiar characteristics that enhance its immunogenic properties.

The CIGB has a vast experience in the production and marketing of vaccines. For Abdala vaccine, we promote business alternatives such as:

- The sale of the vaccine (finished product) for marketing in authorized territories.
- Technology transfer of the formulation, filling and packaging stages, including the sale of the active pharmaceutical ingredient exclusively by the CIGB.
- Design and execution of phase 3 clinical trials.

The Abdala vaccine is supported by intellectual property rights, which claims the design and production of chimeric antigens and composition, which generate a robust immune response when delivered by different administration routes.

Application No. PCT / CU2021 / 050010
International application date:
November 3, 2021

PUBLICATIONS

1. In-solution buffer-free digestion for the analysis of SARS-CoV-2 RBD proteins allows a full sequence coverage and detection of post-translational modifications in a single ESI-MS spectrum. Available in https://www.biorxiv.org/content/10.1101/2021.05.10.443404v1.

2. The SARS-CoV-2 receptor-binding domain expressed in *Pichia pastoris* as a candidate vaccine antigen. Available in https://www.medrxiv.org/content/10.1101/2021.06.29.21259605v1.

3. Elevated antibody titers in Abdala vaccinees evaluated by Elecsys® anti-SARSCoV-2 S highly correlate with UMELISA SARS-CoV-2 ANTI RBD, ACE-2 binding inhibition and viral neutralization assays. Available in https://www.medrxiv.org/content/10.1101/2021.10.18.21265169v1.

4. Safety, tolerability, and immunogenicity of a SARS-CoV-2 recombinant spike protein vaccine: a randomised, double-blind, placebo-controlled, phase 1-2 clinical trial (ABDALA Study). Available in https://www.medrxiv.org/content/10.1101/2021.11.30.21267047v1.

PHARMACEUTICAL FORM
Suspension for injection

ROUTE OF ADMINISTRATION
Intramuscular injection

COMPOSITION
Each 0.5 mL dose contains:
Recombinant protein of the SARS-CoV-2 virus receptor-binding domain (RBD) 0.05 mg
Thiomersal 0.025 mg
Aluminum hydroxide gel
Disodium hydrogen phosphate
Sodium dihydrogen phosphate dihydrate
Sodium chloride
Water for injection, sq

STORAGE CONDITIONS
Abdala vaccine should be stored at 2-8 °C. Do not freeze. Discard vaccine if frozen.

PERIOD OF VALIDITY
9 months

EXPIRATION
The expiration date of the product kept in these conditions is indicated on the label and on the packaging.

THERAPEUTIC INDICATIONS
Abdala is indicated for specific active immunization in adults against SARS-CoV-2 virus infection.

CONTRAINDICATIONS
Children under 2 years of age.

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PRECAUTIONS

The vaccine should not be administered to people who have experienced a severe allergic (anaphylactic) reaction with the previous dose.

Appropriate medical supervision and treatment should always be available in case of an anaphylactic reaction.

Close observation is recommended for at least 15 minutes after vaccination, or a period of time required by the corresponding health authority.

People with chronic, autoimmune or endocrine-metabolic diseases must be compensated at the time of vaccination.

Pre-vaccination vital signs are recommended; in case of arterial hypertension, it is suggested to defer immunization until blood pressure control is not evident.

The efficacy of the vaccine may be lower in immunosuppressed or immunocompromised people.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Convalescents from COVID-19 must follow the vaccination protocol approved for these cases. People may not be fully protected until 14 days after the last dose of the recommended schedule is applied. Like all vaccines, Abdala may not protect everyone who receives it, therefore, vaccinated people must accomplish the anti-epidemic measures recommended by the national health authorities. It contains thiomersal as a preserve, it can cause allergic reactions.

Do not inject the vaccine intravascularly, subcutaneously, or intradermally. In individuals who report acute infection in the last 15 days, inoculation with Abdala should be postponed until resolution of the infection.

DOSAGE AND METHOD OF ADMINISTRATION

Abdala is administered by intramuscular injection in the deltoid region, in three 0.5 mL doses, between 14 days. The time interval between doses should not be shortened.

If the interval between doses is prolonged, a new scheme should not be started, regardless the time that has elapsed since the previous dose application.

In all cases, the specialist will consult the recommendations issued by the health authorities for the vaccine.

ADVERSE EFFECTS

Accumulated clinical experience shows that after the application of the Abdala vaccine in adults, the adverse reactions are mostly mild and being resolved spontaneously without treatment, with a higher occurrence in the first 24-48 hours after administering the vaccine. The frequency of adverse reactions is higher after the application of the first dose of the vaccination schedule and decreases after the subsequent dose application.

According to safety evaluation after the application of 215,267 doses in the clinical trial intervention in risk cohorts, the safety profile previously found in the clinical development was confirmed.

The frequency of adverse reactions in adults is low, between 0.1 and 1% of the total applied doses, mainly local, with a predominance of pain, as well as erythema and induration (0.85%). Systemic adverse reactions include headache (0.54%), somnolence (0.18%), and asthenia (0.14%).

Other adverse reactions with a less than 0.1% frequency of the applied doses have been described, such as nausea, vomiting, arthralgia and general malaise.

In the pediatric population (2-18 years) evaluated in clinical trials, pain at the injection site was the only common or common local adverse reaction (≥ 1% and < 10%). Other local adverse reactions were uncommon (≥ 0.1% and < 1%), such as redness (0.88%) and induration (0.70%). Among the systemic adverse reactions, those reported as common were: headache (2.45%), fever (1.69%) and somnolence (1.23%).

After the application of 13,020,347 doses in the health intervention in populations and territories at risk and subsequent massive vaccination, 5,492 adverse events have been reported (rate of 42.1 x 100,000 doses applied), in which 99.3% are mild.

Only 9 serious adverse events have been reported with a causal relation to vaccination (0.069 x 100,000 administered doses), consisting of an anaphylactic reaction, fully recovered. There are no deaths associated with the Abdala vaccine.

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INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No interaction studies have been performed. Likewise, concomitant administration with other vaccines has not been studied. During clinical research, there was no evidence of drug interactions. The efficacy of vaccination may be affected in patients receiving immunosuppressive therapy. In cases of non-prolonged immunosuppressive treatment, the possibility of postponing vaccination until one month after the end of said treatment should be considered.

USE IN PREGNANCY AND LACTATION

Animal studies do not suggest direct or indirect harmful effects with respect to pregnancy, embryo-fetal development, parturition or postnatal development. The administration of the vaccine in pregnant and lactating women has been well tolerated, accumulating in each group a total of 139,517 and 183,062 doses applied, respectively, without reporting serious adverse events related to the vaccine. Administration during pregnancy should only be considered, based on medical prescription, if the benefits outweigh the known or potential risks to the mother and fetus. The interruption of pregnancy is not necessary in case of vaccinating a woman who does not know her state of pregnancy.

INSTRUCTIONS FOR USE, HANDLING AND DESTRUCTION OF THE UNUSABLE REMAINDER OF THE PRODUCT

Visual inspection the vial before administering the product is recommended. Use the vial with evidence of violating its physical integrity (of the container – closure system) or in case of changes in physical properties (color, transparency, appearance of particles, precipitates) is forbidden.

Shake gently the content of the vial before extracting each dose, to ensure correct homogeneity. Once the vial has been punctured, it must be kept protected from light and stored at 2 to 8 °C, it must not be used after the session is over and the remnants must be discarded. The vial cannot provide a full dose, discard vials with excess volume.

An additional overfill is included in each vial to guarantee 10 doses of 0.5 mL.

The remaining volume of the vaccine from several vials cannot be combined. A separate sterile syringe and needle (23 G o 22 G x 25 mm) should be used for each injection to avoid transmission of infectious agents from one individual to another.

The correct handling and extraction by medical personnel of one or more doses of the vaccine, in a multidose vial, guarantees the quality of the product.

The producer is not responsible for the non-compliance with the recommendations for handling and conservation of the vaccine. This vaccine cannot be used after its expiration date.

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