Ministero della Salute

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Oggetto: indicazioni ad interim sulla strategia vaccinale contro il vaiolo delle scimmie (MPX).

Facendo seguito alla circolare prot. n°35203 del 04/08/2022, visto il Decreto Ministro della Salute del 01/07/2022 con il quale, a seguito di parere positivo da parte del Consiglio Superiore di Sanità e della CTS di AIFA, è stata autorizzata la temporanea distribuzione del vaccino JYNNEOS (MVA-BN), al fine di consentirne la successiva donazione da parte della Commissione Europea, tenuto conto del parere del Gruppo consultivo nazionale sulle vaccinazioni (NITAG - National immunization technical advisory group) in merito alla vaccinazione anti-MPX, si rappresenta quanto segue.

Al momento, la modalità di contagio e la velocità di diffusione, così come l'efficacia delle misure non farmacologiche fanno escludere la necessità di una campagna vaccinale di massa. Tenuto conto dell'attuale scenario epidemico e della limitata disponibilità di dosi, le prime categorie alto rischio a cui verrà offerta inizialmente la vaccinazione, come profilassi pre-esposizione, sono individuate tra:

- personale di laboratorio con possibile esposizione diretta a orthopoxvirus.

- persone gay, transgender, bisessuali e altri uomini che hanno rapporti sessuali con uomini (MSM), che rientrano nei seguenti criteri di rischio:

i) storia recente (ultimi 3 mesi) con più partner sessuali;
e/o
ii) partecipazione a eventi di sesso di gruppo;
e/o
iii) partecipazione a incontri sessuali in locali/club/cruising/saune;
e/o
iv) recente infezione sessualmente trasmessa (almeno un episodio nell'ultimo anno);
e/o
v) abitudine alla pratica di associare gli atti sessuali al consumo di droghe chimiche (Chemsex).

Tali soggetti a più alto rischio potrebbero essere identificati tra coloro che afferiscono agli ambulatori PrEP-HIV dei centri di malattie infettive e dei Check Point, ai centri HIV e ai centri per il trattamento delle malattie sessualmente trasmissibili, utilizzando anche indicatori di comportamento ad alto rischio simili a quelli utilizzati per valutare l'idoneità alla profilassi pre-esposizione all'HIV, ma applicati indipendentemente dalla presenza o meno di infezione da HIV.

Si ritiene importante il coinvolgimento delle associazioni LGBTQIA+ e quelle per la lotta all'HIV, in particolare per favorire una corretta informazione sulla campagna vaccinale.

La strategia di offerta vaccinale a favore di ulteriori gruppi target potrà essere aggiornata sulla base dell'andamento epidemiologico e della disponibilità di dosi.

Il vaccino attualmente disponibile, MVA-BN (virus vaccinico vivo Ankara modificato, non replicante, prodotto dalla Bavarian Nordic), è un vaccino distribuito degli Stati Uniti con il nome di JYNNEOS, e autorizzato dall'FDA per la prevenzione del vaiolo e del vaiolo delle scimmie nei soggetti adulti ad alto rischio di infezione.

MVA-BN è autorizzato anche in Canada, con il nome commerciale IMVAMUNE, e in Europa, con il nome commerciale IMVANEX. Secondo quanto riportato da EMA, tra i due prodotti (JYNNEOS e IMVANEX) esistono piccole differenze in termini di processo di produzione e specifiche di qualità tra le varie autorizzazioni all'immissione in commercio nelle diverse regioni, dovute a differenze nei set di dati, ma che non influiscono sulla qualità finale del vaccino.

Più recentemente EMA ha esteso l'indicazione d'uso di IMVANEX (precedentemente indicato solo per il vaiolo) anche per il vaiolo delle scimmie.

CARATTERISTICHE DEL VACCINO JYNNEOS

JYNNEOS (MVA-BN) è un vaccino indicato per la prevenzione del vaiolo e del vaiolo delle scimmie nei soggetti a partire dai 18 anni di età, ad alto rischio di infezione.

Il vaccino è disponibile in fiale monodose da 0,5 ml.

Posologia

Vaccinazione primaria (soggetti non vaccinati in precedenza contro il virus del vaiolo o con MVA-BN): due dosi (0.5 mL) a distanza di almeno quattro settimane (28 giorni) l'una dall'altra.

Vaccinazione di richiamo: una sola dose (0.5 mL) a chiunque abbia ricevuto in passato almeno una dose di vaccino antivaiolo o di MVA-BN o che abbia concluso il ciclo vaccinale di due dosi di MVA-BN da oltre due anni.

Manipolazione del vaccino e modalità di somministrazione

Relativamente al trasporto e alla conservazione del prodotto si rimanda a quanto già comunicato con nota prot. n°35203 del 04/08/2022 ed eventuali successivi aggiornamenti.

JYNNEOS deve essere scongelato prima dell'uso. Una volta scongelato può essere mantenuto a una temperatura compresa tra +2°C e +8°C, al riparo dalla luce, fino a 12 ore.

Prima dell'uso, attendere che il flaconcino abbia raggiunto una temperatura compresa tra +8 °C e +25 °C e scuoterlo leggermente per almeno 30 secondi. Inoltre, la sospensione deve essere ispezionata visivamente per escludere la presenza di particelle o di alterazioni del colore. Se il flaconcino si presenta in qualsiasi modo danneggiato o se si osservano particelle e/o alterazioni dell'aspetto fisico, il vaccino deve essere eliminato. Il vaccino **non deve essere diluito**.

Prelevare una dose di 0,5 mL con una siringa per preparazioni iniettabili ed eseguire la vaccinazione tramite **iniezione sottocutanea**, preferibilmente nel braccio.

Sicurezza ed efficacia

In generale le reazioni avverse più comuni sono rappresentate da reazioni nella sede di iniezione e reazioni sistemiche comuni tipiche dei vaccini, che si risolvono entro pochi giorni dalla vaccinazione.

Negli studi clinici su JYNNEOS è stato rilevato un tasso di segnalazione di sospette reazioni avverse gravi, tutte non fatali, nell' 1,5%-2,3% dei soggetti vaccinati, contro 1,1% dei soggetti trattati con placebo (con una relazione causale non escludibile per 4 casi).

Relativamente all'efficacia si ritiene che il vaccino MVA-BN sia potenzialmente utile nel proteggere le persone dalla malattia dal virus del vaiolo delle scimmie data la somiglianza tra il virus del vaiolo delle scimmie e il virus del vaiolo (cross-protezione). Studi osservazionali condotti in passato in Africa suggeriscono che l'efficacia dei vaccini antivaiolo nella prevenzione dell'infezione da vaiolo delle scimmie potrebbe raggiungere l'85%. La recente decisione EMA di estendere l'indicazione del vaccino MVA-BN per la protezione contro MPX si è basata sul parere dell'ETF (EMA Task Force) espresso alla luce di risultati di studi di laboratorio (dati non clinici), che suggeriscono che il vaccino induce la produzione di anticorpi diretti contro il virus del vaiolo delle scimmie contribuendo così potenzialmente a proteggere dalla malattia.

Si rappresenta che per il vaiolo delle scimmie non sono ancora stati identificati i correlati immunologici di protezione (ossia il titolo anticorpale necessario per la protezione contro l'infezione o la malattia). Pertanto, l'esecuzione di test di laboratorio (sierologia) successivi alla vaccinazione non è utile per la verifica dell'efficacia della misura di prevenzione.

Sono in corso, a livello globale, studi clinici volti a definire l'efficacia del vaccino MVA-BN nell'attuale contesto epidemico ed eventuale efficacia del suo utilizzo nella profilassi post-esposizione (PEP).

Controindicazioni e avvertenze

Il vaccino è controindicato in caso di ipersensibilità al principio attivo o ad uno qualsiasi degli eccipienti, o residui in tracce. Il vaccino contiene, come eccipienti, trometamolo, sodio cloruro e acqua per preparazioni iniettabili e può contenere residui in tracce quali: proteine di pollo, benzonasi, gentamicina, e ciprofloxacina.

Come per tutti i vaccini iniettabili, devono sempre essere prontamente disponibili i trattamenti e la supervisione medica appropriati nella rara evenienza che si manifestino reazioni anafilattiche dopo la somministrazione del vaccino.

Al momento è preferibile una distanza di almeno 4 settimane (28 giorni) tra la somministrazione di un vaccino anti-SARS-CoV-2/COVID-19 e il vaccino MVA-BN.

Il vaccino, essendo costituito da un virus non replicante, può essere somministrato anche in soggetti immunocompromessi. Tali soggetti potrebbero tuttavia presentare una risposta anticorpale ridotta.

Il vaccino può essere somministrato in soggetti con infezione da HIV o con dermatite atopica.

I soggetti con dermatite atopica, negli studi clinici, hanno sviluppato un maggior numero di sintomi locali e generali dopo la vaccinazione.

Fertilità, gravidanza e allattamento.

Gli studi sugli animali non hanno mostrato alcuna compromissione della fertilità femminile e maschile. I dati relativi all'uso di MVA-BN in donne in gravidanza sono in numero limitato. Tuttavia, gli studi sugli animali non indicano effetti dannosi diretti o indiretti di tossicità riproduttiva. Non è noto se MVA-BN è escreto nel latte materno. A scopo precauzionale, è preferibile evitare l'uso di MVA-BN durante la gravidanza o durante l'allattamento, a meno che non si ritenga che il possibile beneficio in termini di prevenzione superi il potenziale rischio.

Modalità di registrazione della vaccinazione e vaccinovigilanza.

La vaccinazione dovrà essere registrata in anagrafe vaccinale regionale, con le stesse procedure utilizzate per le altre vaccinazioni. In questa prima fase, al fine di monitorare l'andamento della vaccinazione, su richiesta della Direzione Generale della Prevenzione, le Regioni/PA inviano un report contente il numero, range di età, distribuzione per sesso delle persone vaccinate e il numero di dosi somministrate.

Il monitoraggio delle sospette reazioni avverse rientra nelle attività del sistema nazionale di farmacovigilanza. Le segnalazioni di eventuali effetti indesiderati possono essere effettuate direttamente tramite il sistema nazionale di segnalazione (https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse), includendo il numero di lotto.

Si allega, infine, il foglio illustrativo (in lingua inglese) del vaccino JYNNEOS (allegato 1) e la nota informativa (allegato 2).

Il Direttore Generale
**f.to* Dott. Giovanni Rezza

Il Direttore dell'Ufficio 5
Dott. Francesco Maraglio

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**"firma autografa sostituita a mezzo stampa, ai sensi dell'art. 3, comma 2, del d. Lgs. N. 39/1993"*

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use JYNNEOS safely and effectively. See full prescribing information for JYNNEOS.

JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-replicating) suspension for subcutaneous injection
Initial U.S. Approval: 2019

----------INDICATIONS AND USAGE----------
JYNNEOS is a vaccine indicated for prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection. (1)

----------DOSAGE AND ADMINISTRATION----------
For subcutaneous injection only.
Administer two doses (0.5 mL each) 4 weeks apart. (2.1, 2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Suspension for injection. Each dose (0.5 mL) is supplied in a single-dose vial. (3)

----------ADVERSE REACTIONS----------
- In smallpox vaccine-naïve healthy adults, the most common (> 10%) solicited injection site reactions were pain (84.9%), redness (60.8%), swelling (51.6%), induration (45.4%), and itching (43.1%); the most common solicited systemic adverse reactions were muscle pain (42.8%), headache (34.8%), fatigue (30.4%), nausea (17.3%) and chills (10.4%). (6.1)
- In healthy adults previously vaccinated with a smallpox vaccine, the most common (> 10%) solicited injection site reactions were redness (80.9%), pain (79.5%), induration (70.4%), swelling (67.2%), and itching (32.0%); the most common solicited systemic adverse reactions were fatigue (33.5%), headache (27.6%), and muscle pain (21.5%). (6.1)
- The frequencies of solicited local and systemic adverse reactions among adults with HIV-infection and adults with atopic dermatitis were generally similar to those observed in healthy adults. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bavarian Nordic at toll-free phone 1-800-675-9596 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

JYNNEOS is a vaccine indicated for prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection.

2 DOSAGE AND ADMINISTRATION

For subcutaneous injection only.

2.1 Dose and Schedule

Administer two doses (0.5 mL each) of JYNNEOS 4 weeks apart.

2.2 Preparation and Administration

Allow the vaccine to thaw and reach room temperature before use. Once thawed, the vaccine may be kept at +2°C to +8°C (+36°F to +46°F) for 12 hours. Do not refreeze.

When thawed, JYNNEOS is a milky, light yellow to pale white colored suspension.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Swirl the vial gently before use for at least 30 seconds. Withdraw a dose of 0.5 mL into a sterile syringe for injection.

Administer JYNNEOS by subcutaneous injection, preferably into the upper arm (deltoid).

3 DOSAGE FORMS AND STRENGTHS

JYNNEOS is a suspension for injection. Each dose (0.5 mL) is supplied in a single-dose vial.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Allergic Reactions

Appropriate medical treatment must be available to manage possible anaphylactic reactions following administration of JYNNEOS.

Persons who experienced a severe allergic reaction following a previous dose of JYNNEOS or following exposure to any component of JYNNEOS may be at increased risk for severe allergic reactions after JYNNEOS. The risk for a severe allergic reaction should be weighed against the risk for disease due to smallpox or monkeypox.

5.2 Altered Immunocompetence

Immunocompromised persons, including those receiving immunosuppressive therapy, may have a diminished immune response to JYNNEOS.

5.3 Limitations of Vaccine Effectiveness

Vaccination with JYNNEOS may not protect all recipients.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice. There is the possibility that broad use of JYNNEOS could reveal adverse reactions not observed in clinical trials.

The overall clinical trial program included 22 studies and a total of 7,859 individuals 18 through 80 years of age who received at least 1 dose of JYNNEOS (7,093 smallpox vaccine-naïve and 766 smallpox vaccine-experienced individuals).

Solicited Adverse Reactions

Solicited Adverse Reactions in Smallpox Vaccine-Naïve Individuals:

The safety of JYNNEOS in smallpox vaccine-naïve individuals was evaluated in Study 1 [1], a randomized, double-blind, placebo-controlled study conducted in the US in which vaccinia-naïve adults ages 18 to 40 years received either two doses of JYNNEOS (N=3003), or two injections of Tris-Buffered Saline (placebo, N=1002) four weeks apart.

In the total study population, the mean age was 28 years; 47.9% of the subjects were men; 77.4% were white/Caucasian, 17.8% black/African American, 1.9% Asian, 0.5% American Indian/Alaska Native, 0.4% Native Hawaiian/Other Pacific, 1.9% other racial groups; and 11.4% of subjects were of Hispanic/Latino ethnicity. The demographic compositions of JYNNEOS and placebo groups were similar.

In Study 1, subjects were monitored for local and systemic adverse reactions using diary cards for an 8-day period starting on the day of each vaccination. The frequencies of solicited local and systemic adverse reactions following any dose of JYNNEOS are presented in Table 1.

Table 1: Percentages of Subjects with Solicited Local Injection Site Reactions and Systemic Adverse Reactions within 8 Days of Administration of Any Dose of JYNNEOS in Adults 18 to 40 Years of Age, Study 1[x]

Reaction	JYNNEOS N=2943 %	Placebo N=980 %
Local (Injection site)	--	--
Pain	84.9	19.1
Pain, Grade 3[a]	7.4	1.0
Redness	60.8	17.7
Redness ≥ 100 mm	1.5	0.0
Swelling	51.6	5.6
Swelling ≥ 100 mm	0.8	0.0
Induration	45.4	4.6
Induration ≥ 100 mm	0.3	0.0
Itching	43.1	11.7
Itching, Grade 3[b]	1.6	0.2
Systemic	--	--
Muscle Pain	42.8	17.6
Muscle Pain, Grade 3[b]	2.6	0.7
Headache	34.8	25.6
Headache, Grade 3[b]	2.4	2.1
Fatigue	30.4	20.5
Fatigue, Grade 3[b]	3.0	1.3
Nausea	17.3	13.1
Nausea, Grade 3[b]	1.5	1.2
Chills	10.4	5.8
Chills, Grade 3[b]	1.0	0.3
Fever[c]	1.7	0.9
Fever, Grade ≥ 3[c]	0.2	0.0

[X] NCT01144637

[a] Grade 3 pain defined as spontaneously painful

[b] Grade 3 itching, muscle pain, headache, fatigue, nausea and chills defined as preventing routine daily activities

[c] Fever defined as oral temperature ≥ 100.4°F (≥ 38°C), Grade ≥ 3 fever defined as ≥ 102.2°F (≥ 39.0°C)

N=number of subjects

In Study 1, the majority of solicited local and systemic adverse reactions reported with JYNNEOS had a median duration of 1 to 6 days. In general, there were similar proportions of subjects reporting solicited local or systemic reactions of any severity after Dose 2 of JYNNEOS compared with Dose 1, with the exception of injection site pain, which was more commonly reported following Dose 1 (79.3%) than Dose 2 (69.9%).

Solicited Adverse Reactions in Persons Previously Vaccinated with a Smallpox Vaccine:

Three studies (Study 2, Study 3, and Study 4, [2-4]) conducted in the US and Germany evaluated the safety of JYNNEOS in 409 persons previously vaccinated with a smallpox vaccine who received one or two doses of JYNNEOS (mean age 39 years, range 20-80 years; 59% women; 98.8% white/Caucasian; 0.7% Asian; 0.5% black/African American). Subjects were monitored for local and systemic adverse reactions using diary cards for an 8-day period starting on the day of each

vaccination. Across all three studies, solicited local adverse reactions reported following any dose of JYNNEOS were redness (80.9%), pain (79.5%), induration (70.4%), swelling (67.2%), and itching (32.0%) at the injection site; solicited systemic adverse reactions reported following any dose of JYNNEOS were fatigue (33.5%), headache (27.6%), muscle pain (21.5%), nausea (9.8%), chills (0.7%), and fever (0.5%).

Solicited Adverse Reactions in HIV-infected Individuals:

The safety of JYNNEOS in HIV-infected individuals was evaluated in Study 5 [5], an open label trial conducted in the US that included 351 HIV-infected smallpox vaccine-naïve subjects, 131 HIV--infected subjects who previously received smallpox vaccine, 88 non-HIV-infected smallpox vaccine-naïve subjects and 9 non-HIV-infected subjects who had previously received a smallpox vaccine. The racial/ethnic and gender compositions of HIV-infected smallpox vaccine-naïve subjects and those who had previously received smallpox vaccine were similar and overall were 17.0% women; 45.8% white/Caucasian; 0.4% Asian; 33.2% black/African American; 19.0% Hispanic/Latino ethnicity; the HIV-infected smallpox vaccine-naïve group tended to be younger (mean age 37 years) compared to those who had previously received a smallpox vaccine (mean age 45 years). Subjects had CD4 counts ≥ 200 and ≤ 750 cells/μL at study entry.

Solicited local and systemic adverse reactions were reported at similar or lower frequencies in HIV-infected smallpox vaccine-naïve subjects as compared to those seen in non-HIV-infected smallpox vaccine-naive individuals in this study.

In HIV-infected subjects with previous smallpox vaccine exposure, fever and chills were reported in 1.5% and 8.4% of subjects respectively. Frequencies of other solicited local and general adverse reactions in this population were similar to those reported in Studies 2-4 in non-HIV-infected subjects who had previously received smallpox vaccination.

Solicited Adverse Reactions in Individuals with Atopic Dermatitis:

The safety of JYNNEOS in smallpox vaccine-naïve subjects with currently active or a history of atopic dermatitis (AD) was evaluated in a multicenter, open-label clinical study (Study 6 [6]) conducted in the US and Mexico that included 350 subjects with AD and 282 subjects without AD. In the overall study the mean age of subjects was 27 years (range 18-42 years), and subjects were 59.0% women, 39.4% white/Caucasian, 10.9% Asian, 9.0% black/African American, 2.2% Other, and 38.4% Hispanic/Latino ethnicity. Demographic compositions were similar between subjects with and without AD. In subjects with AD, solicited local and systemic adverse reactions were reported at similar frequencies as those in subjects without AD in this study, with the exception of redness (61.2% with AD vs. 49.3% without AD), swelling (52.2% with AD vs. 40.8% without AD), chills (15.9% with AD vs. 7.8% without AD) and headache (47.2% with AD vs. 34.8% without AD).

Serious Adverse Events

The integrated analyses of serious adverse events (SAEs) pooled safety data across 22 studies, which included a total of 7,093 smallpox vaccine-naïve subjects and 766 smallpox vaccine-experienced subjects who received at least 1 dose of JYNNEOS and 1,206 smallpox vaccine-naïve subjects who received placebo only. SAEs were monitored from the day of the first study vaccination through at least 6 months after the last study vaccination.

Among the smallpox vaccine-naïve subjects, SAEs were reported for 1.5% of JYNNEOS recipients and 1.1% of placebo recipients. Among the smallpox vaccine-experienced subjects enrolled in studies without a placebo comparator, SAEs were reported for 2.3% of JYNNEOS recipients. Across all studies, a causal relationship to JYNNEOS could not be excluded for 4 SAEs, all non-fatal, which included Crohn's disease, sarcoidosis, extraocular muscle paresis and throat tightness.

Cardiac Adverse Events of Special Interest

Evaluation of cardiac adverse events of special interest (AESIs) included any cardiac signs or symptoms, ECG changes determined to be clinically significant, or troponin-I elevated above 2 times the upper limit of normal. In the 22 studies, subjects were monitored for cardiac-related signs or symptoms through at least 6 months after the last vaccination.

The numbers of JYNNEOS and placebo recipients, respectively, with troponin-I data were: baseline level (6,376 and 1,203); level two weeks after first dose (6,279 and 1,166); level two weeks after second dose (1,683 and 193); unscheduled visit, including for clinical evaluation of suspected cardiac adverse events (500 and 60).

Cardiac AESIs were reported to occur in 1.3% (95/7,093) of JYNNEOS recipients and 0.2% (3/1,206) of placebo recipients who were smallpox vaccine-naïve. Cardiac AESIs were reported to occur in 2.1% (16/766) of JYNNEOS recipients who were smallpox vaccine-experienced. The higher proportion of JYNNEOS recipients who experienced cardiac AESIs was driven by 28 cases of asymptomatic post-vaccination elevation of troponin-I in two studies: Study 5, which enrolled 482 HIV-infected subjects and 97 healthy subjects, and Study 6, which enrolled 350 subjects with atopic dermatitis and 282 healthy subjects. An additional 127 cases of asymptomatic post-vaccination elevation of troponin-I above the upper limit of normal but not above 2 times the upper limit of normal were documented in JYNNEOS recipients throughout the clinical development program, 124 of which occurred in Study 5 and Study 6. Proportions of subjects with troponin-I elevations were similar between healthy and HIV-infected subjects in Study 5 and between healthy and atopic dermatitis subjects in Study 6. A different troponin assay was used in these two studies compared to the other studies, and these two studies had no placebo controls. The clinical significance of these asymptomatic post-vaccination elevations of troponin-I is unknown.

Among the cardiac AESIs reported, 6 cases (0.08%) were considered to be causally related to JYNNEOS vaccination and included tachycardia, electrocardiogram T wave inversion, electrocardiogram abnormal, electrocardiogram ST segment elevation, electrocardiogram T wave abnormal, and palpitations.

None of the cardiac AESIs considered causally related to study vaccination were considered serious.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically

recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available human data on JYNNEOS administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

The effect of JYNNEOS on embryo-fetal and post-natal development was evaluated in four developmental toxicity studies conducted in female rats and rabbits. In two studies, rats were administered a single human dose of JYNNEOS (0.5 mL) once prior to mating and on one or two occasions during gestation. In the third study, rats were administered a single human dose of JYNNEOS (0.5 mL) on two occasions during gestation. In the fourth study, rabbits were administered a single human dose of JYNNEOS (0.5 mL) once prior to mating and on two occasions during gestation. These animal studies revealed no evidence of harm to the fetus *[see Data]*.

Data

Animal Data
Developmental toxicity studies were conducted in female rats and rabbits. In one study, female rabbits were administered a single human dose of JYNNEOS (0.5 mL) by the subcutaneous route on three occasions: prior to mating, and on gestation days 0 and 14. Three studies were conducted in female rats administered a single human dose of JYNNEOS (0.5 mL) by the subcutaneous route on two or three occasions: prior to mating, and on gestation days 0 and 14; or prior to mating, and on gestation day 0; or on gestation days 0 and 6. No vaccine-related fetal malformations or variations and adverse effects on female fertility or pre-weaning development were reported in these studies.

8.2 Lactation

Risk Summary

It is not known whether JYNNEOS is excreted in human milk. Data are not available to assess the effects of JYNNEOS in the breastfed infant or on milk production/excretion.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for JYNNEOS and any potential adverse effects on the breastfed child from JYNNEOS or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of JYNNEOS have not been established in individuals less than 18 years of age.

8.5 Geriatric Use

Forty-two smallpox vaccine-experienced adults 65 to 80 years of age received at least one dose of JYNNEOS (Study 4).

Clinical studies of JYNNEOS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

When thawed, JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-replicating) is a milky, light yellow to pale white colored suspension for subcutaneous injection.

JYNNEOS is a live vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), an attenuated, non-replicating orthopoxvirus. MVA-BN is grown in primary Chicken Embryo Fibroblast (CEF) cells suspended in a serum-free medium containing no material of direct animal origin, harvested from the CEF cells, purified and concentrated by several Tangential Flow Filtration (TFF) steps including benzonase digestion. Each 0.5 mL dose is formulated to contain 0.5×10^8 to 3.95×10^8 infectious units of MVA-BN live virus in 10 mM Tris (tromethamine), 140 mM sodium chloride at pH 7.7. Each 0.5 mL dose may contain residual amounts of host-cell DNA (≤ 20 mcg), protein (≤ 500 mcg), benzonase (≤ 0.0025 mcg), gentamicin (≤ 0.163 mcg) and ciprofloxacin (≤ 0.005 mcg).

JYNNEOS is a sterile vaccine formulated without preservatives. The vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

JYNNEOS is an attenuated, live, non-replicating smallpox and monkeypox vaccine that elicits humoral and cellular immune responses to orthopoxviruses. Vaccinia neutralizing antibody responses in humans were evaluated to establish the effectiveness of JYNNEOS for prevention of smallpox and monkeypox.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

JYNNEOS has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals. Developmental toxicity studies conducted in rats and rabbits vaccinated with JYNNEOS revealed no evidence of impaired female fertility *[see Use in Specific Populations (8.1)]*.

13.2 Animal Toxicology and/or Pharmacology

The efficacy of JYNNEOS to protect cynomolgus macaques (*Macaca fascicularis*) against a monkeypox virus (MPXV) challenge was evaluated in several studies. Animals were administered Tris-Buffered Saline (placebo) or JYNNEOS (1×10^8 $TCID_{50}$) sub-cutaneously on day 0 and day 28. On day 63, animals were challenged with MPXV delivered by aerosol (3×10^5 pfu), intravenous (5×10^7 pfu) or intratracheal (5×10^6 pfu) route. Across all studies, 80-100% of JYNNEOS-vaccinated animals survived compared to 0-40% of control animals.

14 CLINICAL STUDIES

14.1 Vaccine Effectiveness

Vaccine effectiveness against smallpox was inferred by comparing the immunogenicity of JYNNEOS to a licensed smallpox vaccine (ACAM2000) based on a Plaque Reduction Neutralization Test (PRNT) using the Western Reserve strain of vaccinia virus and was supported by efficacy data from animal challenge studies. *[see Nonclinical Toxicology (13.2)]*

Vaccine effectiveness against monkeypox was inferred from the immunogenicity of JYNNEOS in a clinical study and from efficacy data from animal challenge studies. *[see Nonclinical Toxicology (13.2)]*

14.2 Immunogenicity

Study 7 [7] (N=433) was a randomized, open-label study conducted at US military facilities in South Korea to compare the immunogenicity of JYNNEOS to ACAM2000 in healthy smallpox vaccine-naïve adults 18 through 42 years of age. Subjects were randomized to receive either two doses of JYNNEOS (N=220) administered 28 days apart or one dose of ACAM2000 (N=213). In the total study population, the mean age was 24 years and 23 years in subjects receiving JYNNEOS and ACAM2000, respectively; 82.3% and 86.4% of the subjects were men; 57.3% and 63.8% were white/Caucasian, 21.8% and 18.8% black/African American, 6.4% and 5.6% Asian, 3.6% and 2.8% American Indian/Alaska Native, 2.3% and 1.4% Native Hawaiian/Other Pacific, 8.6% and 7.5% other racial groups, and 24.5% and 18.8% of Hispanic/Latino ethnicity (JYNNEOS and ACAM2000, respectively).

The primary immunogenicity endpoint was geometric mean titer (GMT) of vaccinia neutralizing antibodies assessed by PRNT at “peak visits” defined as two weeks after the second dose of JYNNEOS and four weeks after the single dose of ACAM2000. Analyses of antibody responses were performed in the per-protocol immunogenicity (PPI) population, consisting of individuals who received all vaccinations and completed all visits up until the peak visit without major protocol violations pertaining to immunogenicity assessments. Table 2 presents the pre-vaccination and “peak visit” PRNT GMTs from Study 7.

Table 2: Comparison of Vaccinia-Neutralizing Antibody Responses Following Vaccination with JYNNEOS or ACAM2000 in Healthy Smallpox Vaccine-Naïve Adults 18 through 42 Years of Age, Study 7[x], Per Protocol Set for Immunogenicity[y]

Time Point	JYNNEOS[a] (N=185) GMT[b] [95% CI]	ACAM2000[a] (N=186) GMT[b] [95% CI]
Pre-Vaccination	10.1 [9.9, 10.2]	10.0 [10.0, 10.0]
Post-Vaccination "Peak Visit"[y]	152.8[c] [133.3, 175.0]	84.4[c] [73.4, 97.0]

[x] NCT01913353

[y] Per Protocol Set for Immunogenicity included subjects who received all vaccinations, completed all visits up until the specified "peak visits" (two weeks after the second dose of JYNNEOS or 4 weeks after the single dose of ACAM2000) without major protocol violations pertaining to immunogenicity assessments.

[a] JYNNEOS was administered as a series of two doses given 28 days apart, and ACAM2000 was administered as a single dose.

[b] GMT of vaccinia-neutralizing antibody titers assessed by plaque reduction neutralization test (PRNT) using the Western Reserve vaccinia strain. Values below the assay lower limit of quantitation (LLOQ) of 20 were imputed to a titer of 10; the proportions of subjects with pre-vaccination titers less than the assay lower limit of detection were 98.9% among subjects randomized to JYNNEOS and 97.8% among subjects randomized to ACAM2000, respectively.

[c] Non-inferiority of the "peak visit" PRNT GMT for JYNNEOS compared to ACAM2000 was demonstrated as the lower bound of the 1-sided 97.5% CI for the GMT ratio (JYNNEOS/ACAM2000) was > 0.5.

N: Number of subjects in the specified treatment group; GMT: Geometric Mean Titer; 95% CI: 95% confidence interval, lower limit and upper limit.

PRNT GMTs were also evaluated at pre-specified time points post-vaccination and prior to the "peak visits". The PRNT GMTs at two and four weeks after the first dose of JYNNEOS (prior to the second dose), were 23.4 (95% CI: 20.5, 26.7) and 23.5 (95% CI: 20.6, 26.9), respectively. The PRNT GMT at two weeks after the single dose of ACAM2000 was 23.7 (95% CI: 20.9, 26.8).

15 REFERENCES

1. Study 1: NCT01144637
2. Study 2: NCT00316524
3. Study 3: NCT00686582
4. Study 4: NCT00857493
5. Study 5: NCT00316589
6. Study 6: NCT00316602
7. Study 7: NCT01913353

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Package of 20 single-dose vials (Package NDC number: 50632-001-02; Vial NDC number: 50632-001-01)

16.2 Storage Conditions

Keep frozen at -25°C to -15°C (-13°F to +5°F).
Store in the original package to protect from light.
Do not re-freeze a vial once it has been thawed.
Once thawed, the vaccine may be kept at +2°C to +8°C (+36°F to +46°F) for 12 hours.
Do not use the vaccine after the expiration date shown on the vial label.

17 PATIENT COUNSELING INFORMATION

- Inform vaccine recipient of the potential benefits and risks of vaccination with JYNNEOS.
- Inform vaccine recipient of the importance of completing the two dose vaccination series.
- Advise vaccine recipient to report any adverse events to their healthcare provider or to the Vaccine Adverse Event Reporting System at 1-800-822-7967 and www.vaers.hhs.gov.

Manufactured by:
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DK-3490 Kvistgaard
Denmark

NOTA INFORMATIVA

JYNNEOS (Bavarian Nordic)

Cos'è Jynneos e a cosa serve

Jynneos è un vaccino utilizzato per la prevenzione del vaiolo e del vaiolo delle scimmie (monkeypox).

Jynneos viene somministrato agli individui età pari o superiore a 18 anni. Il vaccino contiene una forma attenuata (indebolita) del virus vaccinico vivo Ankara modificato, non replicante, che appartiene alla stessa famiglia del virus del vaiolo. Jynneos non contiene il virus del vaiolo o del vaiolo delle scimmie. Non è in grado di diffondersi o di causare l'infezione e la malattia del vaiolo o del vaiolo delle scimmie.

Cosa deve sapere prima di ricevere Jynneos

Jynneos non deve essere somministrato in caso di allergia al principio attivo o ad uno qualsiasi degli altri componenti di questo medicinale (elencati di seguito)

Avvertenze e precauzioni

Si rivolga al medico se:

- soffre di dermatite atopica;
- se, a causa di un'infezione da HIV o di una qualsiasi altra malattia o trattamento, il suo sistema immunitario è indebolito.

Altri medicinali e Jynneos

Informi il medico o l'operatore sanitario del centro vaccinale se sta usando, ha recentemente usato o potrebbe usare qualsiasi altro medicinale, o se le è stato somministrato di recente qualsiasi altro vaccino.

Gravidanza e allattamento

Se è in corso una gravidanza, se sospetta o sta pianificando una gravidanza o se sta allattando con latte materno, chieda consiglio al medico prima di ricevere questo vaccino.

Durata della protezione e limitazioni dell'efficacia del vaccino

Sono in corso studi clinici volti a stabilire l'efficacia e la durata della protezione offerta dal vaccino nell'attuale contesto epidemico. Come per tutti i vaccini, la vaccinazione potrebbe non proteggere tutti coloro che lo ricevono.

Come viene somministrato Jynneos

Jynneos viene somministrato sotto forma di iniezione sottocutanea nella parte superiore del braccio. È prevista una seconda dose, non meno di 28 giorni dopo la prima dose.

Se in passato ha già ricevuto la vaccinazione antivaiolosa, riceverà una dose di richiamo.

Possibili effetti indesiderati

Come tutti i vaccini, Jynneos, può causare effetti indesiderati, sebbene non tutte le persone li manifestino.

Gli effetti indesiderati più comuni sono rappresentati da reazioni nella sede di iniezione (rossore, gonfiore, prurito) e reazioni sistemiche comuni tipiche dei vaccini (mal di testa, spossatezza, dolori muscolari, brividi, nausea) che si risolvono entro pochi giorni dalla vaccinazione.

Se soffre già di dermatite atopica possono verificarsi reazioni locali alla pelle più intense (come arrossamento, gonfiore e prurito) e altri sintomi generali (come mal di testa, dolore muscolare, nausea o stanchezza), oltre a un peggioramento delle condizioni della pelle.

In caso di manifestazione di qualsiasi effetto indesiderato, il centro in cui ha effettuato la vaccinazione o si rivolga al medico curante.

Contatti immediatamente un medico o si rechi immediatamente al pronto soccorso dell'ospedale più vicino se dovessero comparire, dopo la vaccinazione, sintomi quali difficoltà a respirare, capogiro, gonfiore del viso e del collo. Tali sintomi potrebbero essere segni di una reazione allergica grave.

È possibile segnalare gli effetti indesiderati direttamente tramite il sistema nazionale di segnalazione (https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse), specificando anche il numero di lotto.

Cosa contiene Jynneos

Il principio attivo è un virus vaccinico vivo Ankara modificato.

Gli altri componenti sono:

- Trometamolo
- Sodio cloruro
- Acqua per preparazioni iniettabili

Possono essere presenti nel vaccino in quantità minime di proteine di pollo, benzonasi, gentamicina, ciprofloxacina.