EMA/2554/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010972/202206

Active substance(s): SARS-CoV-2, spike protein, recombinant, expressed in Sf9 cells derived from spodoptera frugiperda (Nuvaxovid)

Period covered by the PSUR: 20/12/2021 To: 19/06/2022

Centrally authorised Medicinal product(s): For presentations: See Annex A	**Marketing Authorisation Holder**
NUVAXOVID	Novavax CZ, a.s.

Status of this report and steps taken for the assessment[1]

Current step	Description	Planned date	Actual Date
☐	Start of procedure:	15 September 2022	15 September 2022
☐	PRAC Rapporteur's preliminary assessment report (AR)	14 November 2022	14 November 2022
☐	MS/PRAC members and MAH comments	14 December 2022	14 December 2022
☐	PRAC Rapporteur's updated assessment report following comments	29 December 2022	28 December 2022
☐	Oral explanation	n/a	n/a
☒	PRAC recommendation	12 January 2023	12 January 2023

Procedure resources	
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1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for SARS-CoV-2, spike protein, recombinant, expressed in Sf9 cells derived from spodoptera frugiperda (Nuvaxovid).

2. Assessment conclusions and actions

This is the first PSUSA report for NVX-CoV2373 Coronavirus disease (COVID-19) Vaccine (recombinant, Spike Protein, adjuvanted), also referred to as Nuvaxovid. The reporting period covered by this report is 20-Dec-2021 to 19-Jun-2022. The international birth date is 20-Dec-2021.

NVX-CoV2373 is a recombinant, adjuvanted protein vaccine indicated for active immunization to prevent COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in individuals aged 18 years of age and older. NVXCoV2373 is a purified full-length SARS-CoV-2 recombinant (r) spike (S) protein that is stabilised in its prefusion conformation. The addition of the saponin-based Matrix-M adjuvant facilitates activation of the cells of the innate immune system, which enhances the magnitude of the S protein-specific immune response. The two vaccine components elicit B- and T-cell immune responses to the S protein, including neutralizing antibodies, which may contribute to protection against COVID-19.

Cumulatively, a total of 44,823 subjects have been exposed to at least one dose of NVXCoV2373 in the clinical development program as of the data lock point (DLP). Post authorization, as of 19-Jun-2022, 1,034,110 NVX-CoV2373 doses were administered cumulatively in a number of countries including Australia, Canada, EU, Japan, New Zealand, and South Korea.

During the reporting interval, there were no new important identified risk(s). Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) as well as Myocarditis and Pericarditis were considered as important potential risks. At the request of the EMA on 04 March 2022, anaphylaxis was removed as an important potential risk and recharacterised to a risk considered not important for inclusion in the EU RMP V1.1 (submitted 29-Mar-2022). On 03-Aug-2022 (post cut-off date), the validated signal of myocarditis/pericarditis was confirmed and was reclassified from an important potential risk to an important identified risk.

Signal evaluations were completed for anaphylaxis, myocarditis/pericarditis, and paraesthesia for NVX CoV2373. The anaphylaxis and paraesthesia signals have been confirmed; myocarditis/pericarditis had been assessed as indeterminate signal at cut-off date and remained an important potential risk until confirmed as an important identified risk on 03-Aug-2022 (post cut-off date). The product information and RMP have been updated accordingly.

Pursuant to health authorities (HA) inquiries received during the reporting interval, the prespecified AESI of encephalitis/encephalomyelitis and Chest pain/Chest discomfort and Dizziness, became validated signals. These signals have been refuted based on lack of evidence supporting a causal association with NVX-CoV2373.

NVX will continue to monitor safety data from all sources for new emerging signals and changes to known safety concerns according to pharmacovigilance activities established for COVID-19 vaccines. During the reporting interval, there were no actions taken for safety reasons. The overall benefit-risk profile of NVX-CoV2373 remains positive.

It can be concluded that currently, the safety profile of Nuvaxovid is relatively well characterised, although long-term safety remains insufficiently documented. There are various studies in place in the RMP

addressing these issues. This consideration builds on what was described mainly at the time of the conditional marketing authorisation on 20 December 2021 based on the clinical study program, as well as a number of updates undertaken during the post marketing follow-up period. The main updates concern anaphylactic reactions and myocarditis and/or pericarditis. After the DLP of this PSUR, these AESI have been added to Section 4.4 (Special Warnings and Precautions for Use) and Section 4.8 (Undesirable Effects) of the CCDS and respective safety variations for approval of SmPC have been approved/submitted.

The clinical efficacy has been demonstrated in clinical trials. In addition, after the DLP of this report, the product information was updated with data supporting efficacy in adolescents 12 through 17 years of age. Post marketing, no data suggesting lack of efficacy that would constitute a significant risk to the study population were obtained from controlled clinical trials. This, combined with the overall safety profile of NVX -CoV2373 has established a positive benefit-risk profile for the approved indication.

Based on cumulative safety data received and reviewed, the benefit-risk balance of NUVAXOVID remains positive.

3. Recommendations

Based on the PRAC review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of Nuvaxovid remains unchanged and therefore recommends the maintenance of the marketing authorisations.

4. Issues to be addressed in the next PSUR or as a post-authorisation measure (PAM)

The MAH(s) should also address the following issues in the next bimonthly summary safety report (SSR) to be submitted by February 2023

1. It is noted that a number of unlisted adverse reactions of

    a. tinnitus,

    b. dyspnoea and

    c. diarrhoea

    have been reported. The MAH is kindly asked to present an assessment of these reports and is asked whether any revision of the product information is considered necessary.

5. PSUR frequency and other changes to the EURD list

☒No changes to the PSUR frequency

The current **6**-month frequency for the submission of PSURs should remain unchanged.

6. Other considerations

Not applicable

Annex: updated PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This is the first Assessment Report on the Periodic Benefit-Risk Evaluation Report (PBRER) summarising the interval and cumulative safety data received by Novavax (NVX) for the interval covering 20-Dec- 2021 to 19-Jun-2022.

The first marketing authorization for Nuvaxovid was granted in European Union on 20-Dec-2021, which is considered to the be International Birthdate (IBD).

NVX-CoV2373 is a recombinant, adjuvanted protein vaccine indicated for active immunisation to prevent COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS- CoV-2) in individuals aged 18 years of age and older (authorised as COVOVAX in India for ages 7 and older and Thailand for ages 12 and older). In Australia, it (authorised as NUVAXOVID) has also been approved as a booster in adults 18 years of age and older and in New Zealand (authorised as NUVAXOVID) as a heterologous and homologous booster. NVX- CoV2373 is a purified full-length SARS-CoV-2 recombinant (r) spike (S) protein that is stabilised in its prefusion conformation. The addition of the saponin-based Matrix-M adjuvant facilitates activation of the cells of the innate immune system, which enhances the magnitude of the S protein-specific immune response. The 2 vaccine components elicit B-cell and T-cell immune responses to the S protein, including neutralising antibodies, which may contribute to protection against COVID-19. One dose (0.5 milliliters [mL]) contains 5 micrograms (µg) of the SARS-CoV-2 rS protein (produced by recombinant deoxyribonucleic acid [DNA] technology using a Baculovirus expression system in an insect cell line that is derived from Sf9 cells of the *Spodoptera frugiperda*) with 50 µg of the Matrix-M adjuvant. Matrix-M contains Fraction-A (42.5 µg) and Fraction-C (7.5 µg) of *Quillaja saponaria* Molina extract per 0.5 mL dose. NVX-CoV2373 is supplied in a multidose container of 10 doses of 0.5 mL each. The dispersion is colourless to slightly yellow, clear to mildly opalescent with a pH of 7.2. NVX-CoV2373 is administered intramuscularly (IM) as a course of 2 doses of 0.5 mL each. It is recommended to administer the second dose 3 weeks after the first dose.

During the reporting interval, the RSI was updated to the Company Core Data Sheet (CCDS) V 1.0, effective date 01-Mar-2022. Subsequently, the CCDS had two version updates to include the adolescent indication and homologous booster dose following its two-dose primary series, respectively.

1.2. Worldwide marketing authorisation status

NUVAXOVID was first authorised in Indonesia on 31-Oct-2021 and in the EU on 20-Dec-2021.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

During the reporting interval, there were no actions taken for safety reasons.

1.3.2. Changes to reference safety information

The Reference Safety Information (RSI) in effect at the beginning of the reporting interval was the European Union Summary of Product Characteristics (EU SmPC) Version (V) 1.0 effective date 20-Dec-2021.

The following variation procedures are ongoing or completed during the reporting interval.

- Adolescent variation: Submitted 29-Mar-2022, Approved 01-Jul-2022
- SK Bio – DS Manufacturer: Submitted 30-Apr-2022, Approved 04-Jul-2022
- Omicron variation: Submitted 13-Apr-2022, Under Review
- Homologous and Heterologous Boost variation: Submitted 17-May-2022, Under Review
- Shelf-life Extension (9 to 11 months) variation: Submitted 09-Jun-2022, Under Review

During the reporting interval, the RSI was updated to the Company Core Data Sheet (CCDS) V 1.0, effective date 01-Mar-2022. Subsequently, the CCDS had two version updates to include the adolescent indication and homologous booster dose following its two-dose primary series respectively. The current CCDS in effect, is V3.0, effective date 03-May-2022, and it was used for assessing ICSRs in the global vaccine safety database.

Table 1: CCDS Summary of Changes

Version No	Approval Date	Summary of Changes
V1.0	01-Mar-2022	Initial Version
V2.0	21-Mar-2022	Changes in CCDS from V1.0 to V2.0 Therapeutic indication: Age specification under indication was updated from "18 years of age and older" to "12 years of age and older" to include adolescent population in the indication statement. Dosing and method of administration: Dosing and schedule was updated to clarify that there was one dosing regimen for both adolescent and adult populations. The age range of special population was updated to "children 12 years of age and older". Undesirable effects: Supporting data was added about safety in adolescents 12 through 17 years of age. Pharmacodynamic properties: Clinical efficacy was updated with data supporting efficacy in adolescents 12 through 17 years of age.
V3.0	03-May-2022	Changes in CCDS from V2.0 to V3.0 Posology and method of administration: Instructions of use were added under a new subheading of "Booster dose" and "Individuals 18 years of age and older". Undesirable effects and Pharmacodynamic properties: Studies supporting the addition of homologous booster was added. Editorial changes and other minor adjustments to existing text were made.

1.3.3. Estimated exposure and use patterns

Clinical Trial Exposure

Cumulatively, a total of 44,823 subjects were exposed to at least one dose of NVX-CoV2373 from ongoing and completed CTs.

Post-Authorisation Exposure

Cumulatively, as of 19-Jun-2022, 1,034,110 NVX-CoV2373 doses were administered in Australia, Canada, EU, Japan, New Zealand, and South Korea and a total of 49,230,380 NVX- CoV2373 doses (40,010,380 NUVAXOVID and 9,220,000 COVOVAX doses) were distributed globally.

Interval and Cumulative Exposure Data (Distributed and Administered) from Post- Authorisation Experience Presented by Region/LP

Region / License Partner (LP)	Total Doses Administered[a]	Total Doses Distributed[a]
Australia (Biocelect Pty Ltd.)[b]	156,596	6,864,600
Canada (NVX)[b]	5,448	3,238,100
EU (NVX)[b]	288,489	22,479,990
India[c]	N/A	12,000
Indonesia (SIIPL)[c]	N/A	9,008,000
Japan[b]	17,563	3,641,380
New Zealand (Biocelect New Zealand Ltd)[b]	3,904	1,251,600
Singapore[b]	NA	504,000
South Korea (SK Bioscience)[b]	562,110	2,030,710
Thailand (SIIPL)[c]	N/A	200,000
NUVAXOVID Total	**1,034,110**	**40,010,380**
COVOVAX Total	**N/A**	**9,220,000**

Note: Data Sources and cut-off dates are presented in Table 6.
[a] Data presented as recorded.
[b] NUVAXOVID
[c] COVOVAX

1.3.4. Data in summary tabulations

Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

In Study **2019nCoV-101 (Part 1)**, no SAEs or Adverse Events of Special Interest (AESI) have been reported.

In study **2019nCoV-101 (Part 2)**, 44 subjects who received NVX-CoV2373 with Matrix-M adjuvant or placebo experienced a total of 48 SAEs. The most frequent SAEs (5 or more PTs) experienced by subjects fall under the SOCs of Injury, Poisoning and Procedural Complications (9 PTs), Cardiac Disorders (7 PTs), Infections and Infestations (7 PTs), Neoplasms benign, malignant and unspecified (incl cysts and polyps) (7 PTs), and Gastrointestinal Disorders (6 PTs).

In study **2019nCoV-301**, 894 adult subjects and 24 adolescents who received NVX-CoV2373 with Matrix-M adjuvant or placebo experienced a total of 1,536 SAEs. The most frequent SAEs (50 or more PTs) experienced by subjects fall under the SOCs of Infections and Infestations (364 PTs), Cardiac Disorders

(174 PTs), Respiratory, Thoracic and Mediastinal Disorders (128 PTs), Psychiatric Disorders (110 PTs), Injury, Poisoning and Procedural Complications (122 PTs), Neoplasms benign, malignant and unspecified (incl cysts and polyps) (98 PTs), Nervous System Disorders (99 PTs), and Gastrointestinal Disorders (68 PTs).

In study **2019nCoV-302**, 387 subjects who received NVX-CoV2373 with Matrix-M adjuvant or placebo experienced 468 SAEs. The most frequent SAEs (25 or more PTs) experienced by subjects fall under the SOCs of Infections and Infestations (96 PTs), Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps) (77 PTs), Cardiac Disorders (53 PTs), Injury, Poisoning and Procedural Complications (47 PTs), Nervous System Disorders (37 PTs), and Gastrointestinal Disorders (78 PTs).

In study **2019nCoV-311**, no subject experienced Treatment Emergent Adverse Event (TEAE) as of DLP of this PBRER.

In study **2019nCoV-501**, 92 subjects who received NVX-CoV2373 with Matrix-M adjuvant or placebo experienced 99 SAEs. End of study unblinding confirmed that 50 SAEs occurred in the vaccine arm and 49 SAEs occurred in the placebo arm. The most frequent SAEs (10 or more PTs) experienced by subjects fall under the SOCs of Infections and Infestations (23 PTs) and Injury, Poisoning and Procedural Complications (15 PTs), and Pregnancy, Puerperium and Perinatal Conditions (10 PTs).

In study **2019nCoV-505**, two serious Treatment Emergent Adverse Events (TEAE) have been reported as of the DLP of this PBRER.

Cumulative and Interval Summary Tabulations from Post-Authorisation Data

A total 1874 spontaneous ICSRs were received during the 6-month reporting interval (of which 508 ICSRs contained follow-ups), with a total 7857 AEs (767 serious unlisted AEs, 261 serious listed AEs, 3808 non-serious unlisted AEs, and 3021 non-serious listed AEs). There was 1 fatal ICSR reported.

- Of the 158 medically confirmed ICSRs received during the reporting interval, there were 69 serious ICSRs with 171 unlisted AEs (including 1 AE with fatal outcome) and 52 listed AEs, and 89 non-serious ICSRs containing 230 unlisted and 108 listed AEs.
- Of the 1716 non-medically confirmed ICSRs (reporter is not identified as an HCP) received during the reporting interval, there were 274 serious ICSRs with no fatal outcomes, containing 596 unlisted AEs, and 209 listed AEs, and 1442 non-serious ICSRs containing 3578 unlisted AEs, and 2913 listed AEs.

Rapporteur assessment comment:

All ICRS of the reporting period have been evaluated and discussed in detail in previous MSSRs. However, it is noted that a number of reports of tinnitus, dyspnoea and diarrhoea (all unlisted) have been reported. The MAH is kindly asked to present an assessment of these reports and is asked whether any revision of the product information is considered necessary.

1.3.5. Findings from clinical trials and other sources

Completed clinical trial

During the reporting interval, one clinical study was completed for NVX-CoV2373 (2019nCoV-101): Part 1 of a 2-Part, Phase ½ Randomized, Observer-Blinded Study to Evaluate the Safety and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARSCoV- 2-rS) With or Without Matrix M Adjuvant in Healthy Participants. 128 out of 134 participants have completed the study. There were no SAEs or Adverse Events of Special Interest (AESI) reported throughout the study.

Ongoing clinical trials

During the reporting interval, 6 NVX-sponsored CTs were ongoing. There were no emerging safety findings reported from the ongoing CTs. The most recent interim safety, immunogenicity, and efficacy analysis results for ongoing CTs are summarised below.

Study **2019nCoV-301** is an ongoing Phase 3, randomised, observer-blind, placebo-controlled study evaluating the efficacy, safety, and immunogenicity of SARS-CoV-2 recombinant spike protein nanoparticle vaccine with Matrix M adjuvant in adult subjects ≥ 18 years of age in USA and Mexico with a paediatric expansion in adolescents (12 to < 18 years) in the US. The data cut-off for the interim efficacy and safety results for the adult portion of the study was 31-May- 2021 and excludes data from the blinded cross-over period. The study met the prespecified final primary efficacy outcome measure versus (vs) placebo in preventing polymerase chain reaction (PCR)-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination in serologically negative adult subjects. The overall vaccine efficacy (VE) was 90.4%. There were no moderate or severe cases of COVID-19 among subjects who received SARS- CoV-2 rS.

Study **2019nCoV-302** is a phase 3, randomised, observer-blinded, placebo-controlled study evaluating the efficacy, safety, and immunogenicity of two-dose regimen of NVX-CoV2373 (5 µg SARS-CoV-2 rS co-formulated with 50 µg Matrix-M adjuvant), administered 21 days apart in adult subjects 18 to 84 years of age in the UK. The interim safety, efficacy and immunogenicity following the initial set of vaccinations with a data cutoff date of 27-Jul-2021 were presented. The interim results include data from the initial placebo-controlled phase as well as blinded crossover phase that was available at the cutoff date.

Study **2019nCoV-501** is a randomised, observer-blind, placebo-controlled trial evaluating the efficacy, safety, and immunogenicity of a 2-dose regimen of NVX-Cov2373 or placebo administered 21 days apart in South African HIV negative subjects aged ≥ 18 to < 85 years and 233 medically stable PLWH adult subjects aged ≥ 18 to < 65 years old. The Day 236 assessments included analyses of subjects who received a third vaccination (booster) at Day 201 and of subjects who received placebo initially and then crossed over at Day 201 to receive 2 vaccinations of SARS-CoV-2 rS, 21 days apart. Safety was monitored via assessments of unsolicited TEAEs including TEAEs, severe TEAEs, treatment related TEAEs, treatment related severe TEAEs, SAEs, AESI [PIMMCs and COVID-19 related], and MAAEs stratified by baseline serostatus and HIV infection status.

Study **2019nCoV-101 (Part 2)** is the second part of a first-in-human randomised, observer-blind, placebo-controlled trial evaluating the safety and immunogenicity of SARS-CoV-2 rS (5 µg and 25 µg) with or without 50 µg Matrix-M adjuvant in 1,283 healthy adult subjects 18 to 84 years of age.

Study **2019nCoV-505** is a Phase 2, randomised, observer-blind study to evaluate the safety and immunogenicity of NVX-CoV2373 in people living with HIV. No treatment emergent SAEs were reported as of the DLP of this PBRER.

Study **2019nCoV-311** is a Phase 3, randomised, observer-blind study to evaluate the safety and immunogenicity of two booster doses of the NVX-CoV2515 and Bivalent SARS-CoV-2 rS vaccines in adults previously vaccinated with other COVID-19 vaccines. No treatment emergent SAEs were reported as of the DLP of this PBRER.

Long-Term Follow-Up

Subjects enrolled in NVX-sponsored CTs were not subject to long-term safety follow-up.

Other Therapeutic Use of Medicinal Product

During the reporting interval, one compassionate use study was ongoing in South Africa for Health Care Workers (HCW) as part of **2019nCoV-501** study. HCWs were followed for 6 months, and the last visit was a follow-up call to check on their overall health. A total of 99 HCWs were enrolled and 87 of them completed the study. No clinically relevant safety information was reported from the HCW compassionate use portion of the study. HCW data was collected outside of **2019nCoV-501** study.

New Safety Data Related to Fixed Combination Therapies

During the reporting interval, one phase 1/2, randomised, observer-blind study (Study ID: **2019nCoV-ICC-E-101**) to evaluate the safety and immunogenicity of a quadrivalent Nanoparticle Influenza Vaccine (qNIV) and NVX-CoV2373 in healthy subjects ≥ 50 to ≤ 70 years of age is ongoing. No significant safety findings were observed in the ongoing blinded safety review. The final study results were not available as of the DLP of this PBRER.

FINDINGS FROM NON-INTERVENTIONAL STUDIES

No safety findings were reported from any observational, epidemiological, registry and active surveillance programs. During the reporting interval, one Post-authorisation Safety Study (PASS) was ongoing, and no data has been collected or relevant safety information has been received from this study that would impact the benefit-risk assessment of NVX-CoV2373.

As per EMA procedure, EMEA/H/C/005808/MEA/00, feasibility assessments are run on a monthly basis for 2019nCoV-402 study to determine, if there are enough patients vaccinated with Nuvaxovid, within the database, to conduct appropriate analysis. As of DLP, Nuvaxovid doses were not distributed in UK to conduct the feasibility assessment.

Other Clinical Trials

During the reporting interval, there was no relevant new safety observations identified from any other studies for NVX-CoV2373.

Medication Errors

During the reporting interval and cumulatively, the database query identified 43 ICSRs meeting the prespecified search strategy for medication errors. The 43 ICSRs contained a total of 61 AEs. There were 21 non-serious, medically confirmed AEs; 39 non-serious AEs, and 1 serious, non- medically confirmed AE.

Most ICSRs were non-serious (n=42, 97%). Of the total 61 AEs, the most frequently reported AEs were coded to PTs Vaccination error (n=13), Expired product administered (n=8), Product administered to patient of inappropriate age (n=8) and Incomplete course of vaccination (n=5). AEs were reported

alongside medication errors in a small percentage of cases, majority of which were non-serious events falling under different SOCs.

Of the 43 ICSRs, 17 were for females, 19 for males and 7 were of unknown gender; the age range was 9-80 years. The single serious report included the events of inappropriate schedule of vaccine and chest pain. The chest pain developed 2 days after receiving the primary dose and the event outcome was reported as recovering at the time of reporting. No further details were provided. Furthermore, only 9 out of 43 ICSRs were co-reported with AEs.

The reporting rate (rr) was 4.15 per 100,000 doses administered, equivalent to 0.00415% of all doses administered.

NON-CLINICAL DATA

During the reporting interval, there were no safety findings from non-clinical studies that impacted the safety profile of NVX-CoV2373.

LITERATURE

During the reporting interval and cumulatively, 4 literature articles were identified for discussion. Of these, 2 articles compared the immunogenicity of different COVID-19 vaccines (given either as homologous or heterologous regimens). The other 2 articles presented preliminary safety evaluation of NVX-CoV2373 based on reports from Health Authorities in Germany (PEI) and South Korea, respectively.

No new and/or significant safety findings that would impact the overall benefit-risk balance of NVX-CoV2373 was detected.

12 OTHER PERIODIC REPORTS

Periodic reports (monthly summary safety reports, MSSR) were submitted to relevant HA by SII (Covovax) and NVX (Nuvaxovid).

1.3.6. Lack of efficacy in controlled clinical trials

During the reporting interval and cumulatively, no data suggesting lack of efficacy that would constitute a significant risk to the study population were obtained from controlled CTs.

1.3.7. Late-breaking information

Signals

On 27-Jun-2022, pursuant to PRAC request, the prespecified safety topics of "menstrual disorders" and "tachycardia and other rhythm abnormalities" became validated signals. Signal Evaluation Reviews (SER) were included in SSR No.06.

On 29-Jul-2022, pursuant to PMDA request, Acute Coronary syndrome (ACS) became a validated signal, and the SER will be provided in SSR No. 07.

PRAC Rapporteur assessment comment: The signals of tachycardia and other rhythm abnormalities, menstrual disorders, ACS were refuted following detailed assessments in previous SSRs.

Labelling Update

On 21-Jul-2022, CCDS V5.0 was released. Anaphylaxis has been added to Section 4.4 (Special Warnings and Precautions for Use), and both Anaphylaxis and Paraesthesia/Hypoaesthesia have been added to Section 4.8 (Undesirable side effects). The updated Company Core Safety Information (CCSI) was included with SSR No.06 (Data lock 31-Jul-2022).

On 03-Aug-2022, the AESI of myocarditis/pericarditis was reclassified from an important identified risk to an important identified risk. The CCDS and core RMP will be updated accordingly.

PRAC Rapporteur assessment comment: Following DLP of this PSUR the product information was updated with regard the anaphylaxis, paraesthesia/hypoaesthesia and myocarditis/pericarditis.

2. Signal and risk evaluation

2.1. Summary of safety concerns

Summary of Safety Concerns at the Beginning of the Reporting Interval

Risk Criteria	**Description**
Important identified risk(s)	None
Important potential risk(s)	VAED, including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Myocarditis and Pericarditis
Missing information	Use in pregnancy and while breastfeeding Use in immunocompromised patients Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long-term safety

Source: EU Risk Management Plan (EU-RMP) V1.0 dated 20-Dec-2021

At the request of the EMA on 04 March 2022, anaphylaxis was removed as an important potential risk and re-characterised to a risk considered not important for inclusion in the EU RMP.

2.2. Signal evaluation

Tabular overview of signals: new, ongoing or closed during the reporting interval

Signal Term	Date Detected	Status (New, Ongoing, or Closed)	Outcome (Confirmed, Refuted or Indeterminate)	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
Anaphylaxis	18-May-22	Closed	Confirmed	HA Request	Appendix 20	Updated in CCDS v5.0 A safety variation was submitted to EMA for SmPC approval On 01-Aug-2022, a safety variation was submitted to EMA for SmPC approval
Myocarditis and Pericarditis	5-May-22	Ongoing	Confirmed	HA Request	Appendix 21	Pericarditis local label updated for Australia. Planned update to add myocarditis/pericarditis to CCDS and reclassify this as important identified risk in RMP. A safety variation will be submitted by NVX to update SmPC*
Paraesthesia / Hypoaesthesia	27-May-22	Closed	Confirmed	HA Request	Appendix 22	Updated in CCDS v5.0 A safety variation was submitted to EMA for SmPC approval
Encephalitis/ Encephalomyelitis	16-Jun-2022	Closed	Refuted	HA Request	Appendix 23	Signal refuted based on current available data from clinical trials and post- marketing reports
Chest Pain / Chest Discomfort	15-Jun-2022	Closed	Refuted	HA Request	Appendix 24	Signal refuted based on current available data from clinical trials and post- marketing reports
Dizziness	15-Jun-2022	Closed	Refuted	HA Request	Refer to Appendix 25	Signal refuted based on current available data from clinical trials and post- marketing reports

*procedure finalized PDL of this PSUR

Pursuant to HA inquiries received during the reporting interval, the prespecified AESI of encephalitis/encephalomyelitis and MedDRA PTs of Chest pain/Chest discomfort and Dizziness, became validated signals. These signals have been refuted based on lack of evidence supporting a causal association with NVX-CoV2373.

Anaphylaxis

A total of 20 ICSRs were retrieved for the interval and cumulative period. The 20 ICSRs included 20 AEs coded to PTs Anaphylactic reaction (n=15), Circulatory collapse (n=4), and Anaphylactic shock (n=1). All

AEs were designated as serious by convention, of which 2 AEs additionally involved hospitalisation, 1 AE met life threatening (LT) criteria, and 1 AE met other medically important condition criteria. Eleven out of 20 reports were non-medically confirmed.

Of the 20 ICSRs, 1 was for a male and 19 were for females; the age range was 25-55 years with a median age of 39 years. The majority of the ICSRs involved females, who fell in the age group of 35-55 years old (n=13/19, 68%). Almost half of the AEs reportedly occurred within 24 hours of vaccination (n=9, 45%). The O/E analysis was increased for all time windows (0-1 day, 0-2 days, 0-7 days). This was also true if only medically confirmed cases were considered.

PRAC Rapporteur assessment comment: This AESI including signal evaluation has been intensively discussed in the PRAC Assessment reports after evaluation of monthly MSSRs.

Myocarditis and Pericarditis

The 44 ICSRs retrieved for the AESI of myocarditis and pericarditis included a total of 46 AEs coded to PTs Pericarditis (n=32), Myocarditis (n=8), Myopericarditis (n=4) and Carditis (n=2). All 46 AEs were designated as serious by convention, meeting IME criteria, of which 15 AEs additionally involved hospitalisation. Thirty out of 46 AEs were non-medically confirmed. The overall majority of reports were originated from Australia.

Of the 44 ICSRs, 25 were for males and 19 for females; the age range was 19-76 years with a median of 40. The majority of the ICSRs were for 19–29-year-old age group (n=16, 36.3%). In almost half of the reports, the TTO ranged from 0-5 days (n=21, 48%). Individually, for myocarditis (including myopericarditis), there were 7/12 (58%) ICSRs involving females. The age of 6/7 (85.7%) females and 3/5 (60%) males ranged between 19-47 years. Individually, for pericarditis, there were 21/32 (67%) ICSRs involving males. The age of 18/21 (86%) males and 9/11 (82%) females ranged between 19-48 years.

PRAC Rapporteur assessment comment: Results of O/E with sensitivity analyses showed increased RRs for risk windows 0-7 days, 0-14 days, 0-30 days and 0-42 days with the highest RR in the risk window 0-7 days, even when restricted to medically confirmed ICSRs. Age and gender stratified analysis indicated that both sexes are concerned and that apparently younger adults at higher risk, although it is difficult to specify age related risk groups because the number of ICSRs per age group is low. This is in particular true for medically confirmed ICSRs.

Paraesthesia

During the reporting interval and cumulatively, the database identified 252 ICSRs meeting the prespecified search strategy for paraesthesia. The 252 ICSRs contained a total of 314 AEs including 10 serious and 17 non-serious medically confirmed AEs; 28 serious and 259 nonserious, non-medically confirmed AEs. Of the total 314 AEs reported, the most frequently reported PTs included Hypoaesthesia (n=69), Paraesthesia (n=205) and Burning sensation (n=25). The majority of AEs were non-serious, non-medically confirmed (n=259, 82.4%).

Based on the review of the reported ICSRs, paraesthesia was generally described one of two clinical scenarios: either paraesthesia as a subset of generalised symptoms consistent with systemic reactogenicity, or paraesthesia associated with localised neuromotor symptoms. Associated generalised symptoms included headache, fever, rash, pain (including abdominal pain), nausea, vomiting, diarrhoea, fatigue, dizziness, brain fog, chest pain, and palpitations. Reports describing paraesthesia alone or in

association with neurologic or motor symptoms included lymphadenopathy, rash, pain or swelling limited to the affected limbs. Two reports of facial nerve palsy were associated with paraesthesia and/or hypoesthesia, though one report indicated that the patient also had a possible shingles outbreak. No pattern was evident to suggest paraesthesia as a sign or symptom of progressive polyneuropathy.

The reporting rate (rr) was 24.37 per 100,000 doses administered.

Encephalitis and Encephalomyelitis

Based on the request of the authority in South Korea the MAH performed a specific query. A single ICSR was retrieved for the interval and cumulative period. The single ICSR included 1 AE coded to PT Non-infective encephalitis (n=1). This AE was designated as serious by convention.

This report concerned a 42-year-old female who experienced non-infective encephalitis (unknown TTO) with co-reported events of confusional state, diarrhoea, migraine, muscle twitching and pyrexia. The event outcome of non-infective encephalitis was reported as unknown. The single report of encephalitis did not contain information regarding the clinical status of the patient, physical examination findings or diagnostic workup, thus the case is considered Level 4 B criteria for encephalitis.

PRAC Rapporteur assessment report: A single ICSR (BC L 4) does not support a signal. It is agreed upon that the signal was closed and refuted.

Chest Pain/Chest Discomfort

As of the DLP of SSR No. 05 (30-Jun-2022), there were 298 ICSRs of chest pain and/or chest discomfort reported, with a majority of events experienced within 5 days of vaccination, and a majority reported from Australia. There were 25 ICSRs (8.4%) with a seriousness criterion of hospitalisation, life threatening, or disability (not including additional cases that were serious by convention due to IME criteria). Twelve of those ICSRs were cases of myocarditis and/or pericarditis cases and were assessed against a case definition of myocarditis and/or pericarditis.

Overall, findings of this cumulative review and co-reported AEs suggest no apparent patterns or trends that would identify specific diagnoses beyond the chest pain/discomfort that may potentially relate to listed events or other topics under review (hypersensitivity, vaccination anxiety-related events and myocarditis/pericarditis).

Dizziness

A signal of dizziness was validated on 15-Jun-2022 after a request was received from Health Canada in their assessment of 3rd monthly safety update report (period covering 01-Apr-2022 to 30-Apr-2022). A complete signal evaluation was performed after the data cut-off, based on which this signal was refuted.

As of the DLP of SSR No. 05 (30-Jun-2022), a total of 253 post-marketing ICSRs were retrieved. The majority of ICSRs (89%) were non-serious with 29 (12%) meeting serious criteria. Of those meeting serious criteria, 15 (51%) were due to hospitalisation, and 5 (17%) were medically confirmed. Events were most frequently reported from Germany (45%) and Australia (39%).

Time to onset was reported in 176 (70%) cases, occurring most commonly between day 0 and day 5. Dizziness was reported most often by females, in 70% of total events. Co-reported multi-system symptoms were frequently reported, including headache, nausea, diarrhoea, tachycardia, fatigue,

pain/chest pain, myalgia, dyspnoea, paraesthesia (pins and needles). In most cases, this constellation of co-reported symptoms may be associated with reactogenicity, or anxiety, and do not suggest a specific neurologic pattern.

Limited information was provided in most of these reports, including lack of medical history and concomitant medication. No medical treatment was reported for dizziness.

Other Safety Topics Not Considered as Signals

AESI

ICSRs with MedDRA PTs related to the following AESI search strategies have been identified across interval and cumulative data:

- Anaphylaxis: see chapter 2.2. above
- Myocarditis and Pericarditis see chapter 2.2 above

For each of the following AESIs, one case was reported during the period covered by the PSUR (and cumulatively post marketing.

- Autoimmune Thyroiditis, Cerebral Venous Sinus Thrombosis, Chronic Fatigue Syndrome, Encephalitis, Encephalomyelitis, Fibromyalgia, Haemorrhagic Stroke, Optic Neuritis, Postural Orthostatic Tachycardia Syndrome

For Guillain-Barré Syndrome cumulatively two ICSRs were reported. For each of the following AESIs 3 ICSRs were cumulatively reported:

- Ischaemic stroke, multiple sclerosis (thereof 2 reports of MS relapse), Rheumatoid Arthritis (thereof 2 cases aggravation of pre-existing disease)

For the remaining AESIs the following number of ICSRs were reported.

AESI	No. cumulative ICSRs (n=)	Comment	O/E analysis result
Bell's Palsy	7		O/E analysis showed that observed exports are lower than expected; result of sensitivity analysis with the assumption of 75 % underreporting RR 2.53 (95% CI 1.09-4.98)
Generalised Convulsions	5	Reported as seizure (n=3), colonic convulsions (n=1), febrile convulsion (n=1)	O/E analysis + sensitivity analyses do not suggest a signal

Myocardial Infarction (MI)	8	Reported as troponin increased (n=5), MI (n=3)	O/E analysis + sensitivity analyses do not suggest a signal
Thrombocytopenia	5		O/E analysis + sensitivity analyses do not suggest a signal
Venous Thromboembolism	9	Pulmonary embolism (n=4), thrombophlebitis (n=3), DVT (n=1), SVST (n=1)	O/E analysis + sensitivity analyses do not suggest a signal

Sensitivity analyses of O/E considered 25 % and 75 % underreporting

Spontaneous Abortion: Four ICSRs reporting spontaneous abortion have been reported. A meaningful analysis could not be performed as vaccination with respect to pregnancy was mostly not reported except for one report where a female at gestational period of 1 month presented with paraesthesia and spontaneous abortion. Other details like obstetric and medical history, concomitant medications, and further details were lacking. Hence the available information was not suggestive of a causal association between the event and vaccine. No safety signal was identified.

Rapporteur assessment comment:

In general, the number of AESIs (exception anaphylaxis, myocarditis/ pericarditis) and the available clinical information concerning these ICSRs do not raise a concern/ signal.

2.3. Evaluation of risks and safety topics under monitoring

Additional Safety Topics for Monitoring

The global vaccine safety database was queried for the cumulative period up to 19-Jun-2022 according to the prespecified search strategies for the safety topics listed below.

Fatal reports

One ICSR was received. This report concerned a 96-year-old male with medical history of cerebrovascular accident, congestive heart disorder, atrial fibrillation, dementia with Lewy bodies, Parkinson's disease, and type 2 diabetes mellitus. Due to lacking TTO, a temporal relationship could not be identified. No other relevant information was reported. No new information was received upon follow-up.

Experience in special patient populations (paediatric and elderly age groups)

- Paediatric population

During the reporting interval and cumulatively, the database query identified 12 ICSRs involving paediatric patients (<18 years of age) which contained a total of 25 AEs including 3 non-serious, medically confirmed AEs; and 22 non-serious, non-medically confirmed AEs. The most frequently reported PTs were Vaccination error (n=11) and Product administered to the patient of inappropriate age (n=8). Of

the 12 ICSRs, 8 were for males, 3 for females and 1 was of unknown gender; the age range was 9-17 years. The majority of the AEs were non-medically confirmed and non-serious (22, 73.4%). No other significant details were reported for the majority of ICSRs.

- Elderly groups

During the reporting interval and cumulatively, the database query identified 145 ICSRs involving elderly patients (≥ 65 years of age) which contained a total of 500 AEs including 1 fatal, 31 serious and 38 non-serious, medically confirmed AEs; and 49 serious and 381 nonserious, non-medically confirmed AEs.

The most frequently reported PTs were Headache (n=31), Fatigue (n=25) and Myalgia (n=19). Of the 145 reports, 40 were for males and 100 for females; the age range was 65-96 years. TTO ranged from 0-61 days when reported (n=87) and in half of the reports, it ranged within 0-10 days (n=74, 51%). Of the total 500 AEs reported, most of the AEs were non-serious, nonmedically confirmed (n=381, 76.2%). The outcome of the majority of the events were reported as not recovered at the time of reporting. No significant medical history or concomitant medications were reported for the majority of the ICSRs.

Vaccine anxiety-related reactions

During the reporting interval and cumulatively, the database query identified 22 ICSRs of vaccine anxiety-related reactions which contained a total of 22 AEs coded to PTs Anxiety (n=16), Nervousness (n=3), Agitation (n=2), and Tension (n=1) including 2 non-serious, medically confirmed AEs; and 1 serious and 19 non-serious, non-medically confirmed AEs. Of the 22 reports, 2 were for males and 20 for females; the age range was 27-62 years. The TTO ranged from 0-17 days when reported (n=14). No significant medical history or concomitant medications were reported for the majority of ICSRs.

PRAC Rapporteur assessment comment: The terms "anxiety" and" stress-related reactions" are mentioned in section 4.4 of the SmPC. It may be useful to mention examples of such reactions e.g. dizziness (n=250 AEs), palpitations (n=127 AEs), tachycardia (n=103) etc. For the next PSUR: The MAH may consider to update the product information regarding adverse events which may reflect anxiety or stress-related reactions.

Cholecystitis

During the reporting interval and cumulatively, the database query identified 6 ICSRs meeting the prespecified search strategy for cholecystitis which contained a total of 6 AEs including 1 serious, medically confirmed; 4 non-serious and 1 serious, non-medically confirmed. The reported PTs were Abnormal faeces (n=2) and Jaundice (n=2), faeces pale (n=1) and blood bilirubin increased (n=1). Of the 6 ICSRs, 3 were for males and 3 for females; the age range was 23-54 years. TTO ranged from 0- 12 days when reported (n=4). Three ICSRs were from Australia, 2 from Germany and 1 from New Zealand.

The rr was 0.58 per 100,000 doses administered, equivalent to 0.00058% of all doses administered.

PRAC Rapporteur assessment comment: The MAH presented some clinical information for 3 reports (jaundice, blood bilirubin increase), which do not suggest cholecystitis. In one case liver biopsy revealed drug/toxin-induced injury, in one case in a Crohn's patient developed little jaundice, intestinal bleeding, hypotension and the third report is unclear. The two non-serious report from Germany only mentioned stool abnormalities (if correctly identified in EudraVigilance). The diagnosis of cholecystitis is questionable in all 6 ICSRs.

Inflammatory eye disorders

During the reporting interval and cumulatively, the database query identified 33 ICSRs meeting the prespecified search strategy for inflammatory eye disorders which contained a total of 38 AEs including 2 non-serious medically confirmed AEs, 34 non-serious, non-medically confirmed and 2 serious non-medically confirmed AEs.

The most frequently reported PTs were Eye swelling (n=9), Lacrimation increased (n=5), Ocular hyperaemia (n=4) and Photophobia (n=5). Of the 33 reports, 26 were for females and 7 for males; the age range was 26-61 years. The TTO for most of these reports ranged from 0-3 days (n=13). Most of the AEs were non-serious, non-medically confirmed (n=34, 89.47%). The majority of the events were reported as not recovered at the time of reporting. Medical history in these reports included seasonal allergy (n=4), asthma (n=2) and Basedow's disease (n=2). No other significant details were provided.

The reporting rate was 3.19 per 100,000 doses administered, equivalent to 0.00319% of all doses administered.

Menstrual disorders

During the reporting interval and cumulatively, the database query identified 66 ICSRs meeting the prespecified search strategy for menstrual disorders which contained a total of 104 AEs including 1 serious, medically confirmed AE; and 5 serious and 98 non-serious non-medically confirmed AEs. The age of these females ranged from 20 to 53 years. TTO ranged from 0-35 days when reported (n=37). Of the total 104 AEs reported, the predominantly reported PTs included Menstrual disorder (n=37), Heavy menstrual bleeding (n=18), Menstruation irregular (n=10), Amenorrhea (n=9), Dysmenorrhea (n=9), Intermenstrual bleeding (n=7). Most of the AEs were non-serious, nonmedically confirmed (n=98, 94%).

The rr was 6.38 per 100,000 doses administered.

Paraesthesia (see chapter 2.2)

Reactogenicity profile- second dose and boosters (based on impurity levels)

During the reporting interval and cumulatively, the database query identified 76 ICSRs meeting the prespecified search strategy for reactogenicity profile-second dose and boosters which contained a total of 450 AEs. Of these 76 ICSRs, one report with a missing batch number was excluded from the analysis.

The most frequently reported PTs were coded to Headache (n=34), Fatigue (n=27), Pyrexia (n=25), Limb discomfort (n=19) and Injection site pain (n=17). Of the 76 ICSRs, 54 were for females and 22 for males; the age range was 21-93 years. TTO from second dose or boosters ranged from 0-24 days. The majority of the AEs were non-medically confirmed; non-serious (n=354, 77.8%) with most of the outcomes reported as recovering; recovered at the time of reporting.

No batch related issues were identified in any of the reports. The rr was 7.35 per 100,000 doses administered. A review of ICSRs did not identify any trend related to reactogenicity based on impurity levels specifically after a second dose and/or a booster. No safety signal was identified.

New Information on Important Potential Risks

Vaccine-Associated Enhanced Disease (VAED), Including Vaccine-Associated Enhanced Respiratory Disease (VAERD):

During the reporting interval and cumulatively, no ICSRs were retrieved.

Anaphylaxis:

A signal of anaphylaxis was validated on 18-May-2022.

Most reports retrieved for the interval and cumulative period, have originated from HAs (n=19/20). 13/20 reports were from TGA.

Myocarditis and Pericarditis:

A signal of myocarditis/pericarditis was validated on 05-May-2022 based on HA requests and statistically significant results of O/E analyses in the cumulative period.

All reports retrieved (n=44) for the interval and cumulative period, have originated from Has. 36/44 reports were from TGA. Following the cut-off date of 19-Jun-2022, myocarditis/pericarditis was confirmed as an important identified risk.

New Information on Important Identified Risks

During the reporting interval and cumulatively, there were no important identified risk(s) for NVX-CoV2373.

Vaccination Failures / Lack of efficacy

During the reporting interval and cumulatively, the database query identified 1 ICSR meeting the prespecified search strategy for vaccination failures / lack of efficacy. This report contained a non-serious, non-medically confirmed AE coded to PT Paradoxical drug reaction (n=1) occurring in a 27-year-old female.

The event occurred 2 days after the primary dose of the vaccine. Since the full dose schedule was not completed, this report was assessed as not a vaccination failure.

Update on Missing Information Topics

Use in Pregnancy and While Breastfeeding:

Use in Pregnancy: During the reporting interval and cumulatively, the database query identified 4 ICSRs meeting the prespecified search strategy for use in pregnancy. The 4 ICSRs involving pregnancy identified a total of 5 AEs coded to PTs Abortion spontaneous (n=4) and Paraesthesia (n=1) including 4 serious and 1 non-serious, non-medically confirmed AEs. All 4 reports were retrospective in nature. Age of the females ranged from 23-31 years. In one report, a female at 1 month gestation, presented with paraesthesia 2 days after vaccination and subsequently experienced spontaneous abortion 2 weeks later. No other significant details were provided in this report. For all other ICSRs, an analysis could not be performed as timing of gestational age, obstetric details, medical history, concomitant medication, and further details were unknown.

Use while breastfeeding: During the reporting interval and cumulatively, the database query identified 2 ICSRs meeting the prespecified search strategy for use while breastfeeding. The 2 ICSRs identified a total of 2 AEs coded to PTs Lactation puerperal increased (n=1) and Suppressed lactation (n=1). Both AEs

were non-serious and non-medically confirmed. The event outcomes in the two reports were recovered and not recovered respectively.

The reports of use in pregnancy and use during breastfeeding did not raise any safety concerns. No safety signal was identified.

Use in Immunocompromised Patients:

Three ICSRs in immunocompromised individuals were received. Review of individual reports did not suggest a new safety signal.

Use in Frail Patients with Comorbidities:

During the reporting interval and cumulatively, as of 19-Jun-2022, the database query identified 244 ICSRs meeting the prespecified search strategy for use in frail patients with comorbidities. The 244 ICSRs reported a total of 1,224 AEs including 55 serious and 36 non-serious, medically confirmed AEs and 173 serious and 960 non-serious, non-medically confirmed AEs. The most frequently reported PTs were Dizziness (n=35), Chest pain (n=29), Dyspnoea (n=28), Paraesthesia (n=26) and Tachycardia (n=23). Of the 244 ICSRs, 189 were for females (77%), and 54 (22%) for males; the age range was 19-96 years. Most reports were of individuals above the age of 40 years (n=166, 68%). The outcome of majority of events was reported as not recovered at the time of reporting. No safety signal was identified.

Use in Patients with Autoimmune or Inflammatory Disorders:

During the reporting interval and cumulatively, the database query identified 108 ICSRs meeting the prespecified search use in patients with autoimmune or inflammatory disorders. The 108 ICSRs reported a total of 612 AEs including 7 serious and 12 non-serious, medically confirmed AEs; and 103 serious and 490 non-serious, non-medically confirmed AEs. The most frequently reported PTs were Headache (n=39) and Fatigue (n=28). Of the 108 ICSRs, 97 (89%) were for females and 11(10%) for males; the age range was 21-85 years Most reports were of individuals above the age of 40 years (n=71, 65%). The TTO ranged from 0-28 days. No safety signal was identified.

Interaction with Other Vaccines:

During the reporting interval and cumulatively, no ICSR was retrieved.

Long-Term Safety:

Long-term safety is evaluated by routine monitoring of Post-Authorisation Safety Studies (PASS). No patients have been enrolled in the current PASS studies since the authorisation of NVXCoV2373.

Rapporteur assessment comment:

No further action is considered warranted at this stage

2.4. Characterisation of risks

During the reporting period new safety signals have been identified: anaphylaxis, paraesthesia/hypoaesthesia and myocarditis/ pericarditis. Post DLP the product information has been updated with regard to these signals.

Effectiveness of Risk Minimisation

Routine risk minimisation measures are in place for NVX-CoV2373; there are no additional risk minimisation measures in place.

3. Benefit evaluation

The efficacy of NVX-CoV2373 has been established in 2 pivotal phase III studies, supported by pre- and post-crossover study designs. Pooled efficacy conclusions from the interim analysis of two pivotal phase III randomised, double-blind, placebo-controlled trials evaluating the efficacy, safety and immunogenicity of two-dose regimen of NVX-CoV2373 administered 21 days apart in adults (2019nCoV-301 adults and 2019nCoV302) and adolescents (2019nCoV-301 adolescents Substudy) are summarised below:

- Overall NVX-CoV2373 prevented PCR-confirmed symptomatic moderate or severe COVID-19 in serologically negative adult and adolescent subjects.
- In adults, NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID-19 due to SARS-CoV-2 variant considered or not considered a VOC or VOI with onset from at least 7 days after second vaccination in serologically negative adult subjects.
- In adults, NVX-CoV2373 prevented PCR-confirmed symptomatic moderate or severe COVID-19 with onset from at least 7 days after second vaccination in serologically negative (to SARS-CoV-2) adult subjects.
- In adults, NVX-CoV2373 prevented PCR-confirmed any symptomatic SARS-CoV-2 infection with onset from at least 7 days after second vaccination in serologically negative (to SARS-CoV-2) adult subjects, with results similar to those of the primary efficacy endpoint (VE = 90.55% (95% CI: 83.16, 94.70).
- In adolescents, VE was 79.54% for the primary endpoint and most cases were mild in severity.
- In adolescents, VE was 82.04% due to a SARS-CoV-2 variant considered as a VOC/VOI, which was represented only by the Delta VOC.
- In adolescents, NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID19 with onset from at least 7 days after second vaccination in adolescent subjects regardless of baseline serostatus with results similar to those of the primary efficacy endpoint.
- In adolescents, NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID19 with onset from first injection in adolescent subjects regardless of baseline serostatus.

Long term follow-up data are not currently available and safety and efficacy of NVX-CoV2373 has not been studied in pregnant and breastfeeding women, immunocompromised patients (except PLWH) and patients with autoimmune or immunodeficiencies. Post-authorisation studies will further characterise this missing information.

Evidence from interim analysis of two pivotal phase III CTs suggested that NVX-CoV2373 was shown to be safe and effective in preventing PCR confirmed COVID-19 infections, when a two- dose series was administered 21 days apart in adults (2019nCoV-301 and 2019nCoV302) and adolescents (2019nCoV-301 adolescents sub study).

There are no new data on efficacy that alters previous assessments, and which are described in the approved product information.

4. Benefit-risk balance

The Clinical benefit demonstrated in clinical trials, combined with overall safety profile of NVX -CoV2373 has established a positive benefit-risk profile for the approved indication.

In CTs, administration of NVX-CoV2373, with or without Matrix-M adjuvant was well tolerated in ages 12 years and above.

Six signals from the post-authorization setting were validated and reviewed during the reporting interval. Anaphylaxis and paraesthesia/hypoaesthesia were confirmed and CCDS has been updated.

On 03-Aug-2022 (post cut-off date), the validated signal of myocarditis/pericarditis was confirmed and was reclassified from an important potential risk to an important identified risk.

Signals of chest pain/chest discomfort, dizziness and encephalitis/encephalomyelitis have been refuted as signals.

NVX-CoV2373 is under additional monitoring due to conditional marketing authorisation, new active substance and new biological.

The overall benefit-risk balance for NVX-CoV2373 remains positive.

5. Rapporteur Request for supplementary information

2. It is noted that a number of unlisted adverse reactions of

    a. tinnitus,

    b. dyspnoea and

    c. diarrhoea

    have been reported. The MAH is kindly asked to present an assessment of these reports and is asked whether any revision of the product information is considered necessary.

6. MAH responses to Request for supplementary information

MAH response: The request for assessment of reports of Tinnitus, Dyspnoea and Diarrhoea is acknowledged. The assessments will be completed and summarized in the 2nd bi-monthly summary safety report (SSR) to be submitted by February 2023.

7. Comments from Member States

Member states' comments: no additional comments, endorsement from 2 MS