ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

BIMERVAX emulsion for injection
COVID-19 Vaccine (recombinant, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial which contains 10 doses of 0.5 mL

One dose (0.5 mL) contains 40 micrograms of SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion heterodimer* (B.1.351 and B.1.1.7 strains) adjuvanted with SQBA.

*Produced by recombinant DNA technology using a plasmid expression vector in a CHO cell line.

SQBA adjuvant containing per 0.5 mL dose: squalene (9.75 mg), polysorbate 80 (1.18 mg), sorbitan trioleate (1.18 mg), sodium citrate (0.66 mg), citric acid (0.04 mg) and water for injections.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Emulsion for injection (injection)
White homogeneous emulsion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BIMERVAX is indicated as a booster for active immunisation to prevent COVID-19 in individuals 16 years of age and older who have previously received a mRNA COVID-19 vaccine (see sections 4.2 and 5.1).

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 16 years of age and older
A single intramuscular dose (0.5 mL) of BIMERVAX should be administered. There should be an interval of at least 6 months between prior receipt of a mRNA vaccine and administration of BIMERVAX (see section 5.1).

Elderly population
No dose adjustment is required in elderly individuals ≥ 65 years of age.

Paediatric population
The safety and efficacy of BIMERVAX in children and adolescents less than 16 years of age have not been established yet. No data are available.

Method of administration

BIMERVAX is for intramuscular administration only, preferably into the deltoid muscle of the upper arm.

Do not administer this vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported with COVID-19 vaccines. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia), because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of BIMERVAX may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with BIMERVAX may not protect all vaccine recipients.

Excipients

Potassium
This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

Sodium
This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of BIMERVAX with other vaccines has not been studied.

4.6 Fertility, pregnancy, and lactation

Pregnancy

There is no experience with the use of BIMERVAX in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition, or post-natal development (see section 5.3).

Administration of BIMERVAX during pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breast-feeding

It is unknown whether BIMERVAX is excreted in human milk.

No effects on the breast-fed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to BIMERVAX is negligible.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, see section 5.3.

4.7 Effects on ability to drive and use machines

BIMERVAX has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions reported were injection site pain (82.2%), headache (30.2%), fatigue (30.9%) and myalgia (20.2%). The median duration of local and systemic adverse reactions was 1 to 3 days. Most adverse reactions occurred within 3 days following vaccination and were mild to moderate in severity.

Tabulated list of adverse reactions

The safety profile presented below is based on interim pooled safety data generated in two phase 2b and phase 3 clinical trials with a total of 3 192 individuals 16 years of age and older, that received one booster dose of BIMERVAX at least 3 months after a previous COVID-19 vaccine. The median duration of the safety follow-up was 5 months for a 84% of the individuals, and 7.5 months for a 16% of the individuals.

Adverse reactions observed during clinical trials are listed below according to the following frequency categories: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10 000 to < 1/1000), very rare (< 1/10 000) and not known (cannot be estimated from the available data).

Table 1: Adverse reactions

System organ class	Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders		Lymphadenopathy[a]			
Psychiatric disorders			Insomnia		
Nervous system disorders	Headache		Dizziness Somnolence	Paraesthesia Hypoaesthesia	
Cardiac disorders					Pericarditis[c]
Gastrointestinal disorders		Diarrhoea Vomiting Nausea	Odynophagia Abdominal pain[b]		
Skin and subcutaneous tissue disorders			Pruritus	Urticaria Cold sweats Rash Erythema	
Musculoskeletal and connective tissue disorders	Myalgia		Arthralgia	Back pain	
General disorders and administration site conditions	Injection site pain Fatigue	Injection site swelling Injection site erythema Injection site induration Pyrexia Axillary pain	Asthenia Chills Malaise Injection site pruritus Injection site hypersensitivity	Injection site bruising	

[a] This term also included events reported as lymphadenitis
[b] This term also included events reported as upper and lower abdominal pain
[c] Based on a single event during clinical trials

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Covid-19 vaccines, ATC code: J07BN

Mechanism of action

BIMERVAX is a recombinant protein vaccine whose active substance (antigen) is SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion heterodimer – B.1.351-B.1.1.7 strains. Following administration, an immune response is generated, both at a humoral and cellular level, against the SARS-Co-V-2 RBD antigen. Neutralising antibodies against the RBD domain of SARS-CoV-2 prevent RBD binding to its cellular target ACE2, thus blocking membrane fusion and viral infection. Moreover, BIMERVAX induces antigen-specific T-cell immune response, which may contribute to protection to COVID-19.

Efficacy

Efficacy of BIMERVAX has been inferred by immunobridging of immune responses to an authorised COVID-19 vaccine, for which vaccine efficacy has been established.

Immunogenicity

The immunogenicity of BIMERVAX was evaluated in one pivotal phase 2b multi-centre clinical trial (Study HIPRA-HH-2) and in one phase 3 multi-centre clinical trial (Study HIPRA-HH-5).

Study HIPRA-HH-2
Study HIPRA-HH-2 is an ongoing phase 2b, double-blind, randomised, active-controlled, multi-centre, non-inferiority clinical trial to assess immunogenicity and safety of a booster vaccination with BIMERVAX compared to tozinameran/COVID-19 mRNA Vaccine, in adults fully vaccinated against COVID-19 with a mRNA vaccine at least 6 months before enrolment. This phase 2b clinical trial excluded individuals who were pregnant, individuals who were immunocompromised or had received immunosuppressants within 12 weeks, as well as individuals with previous COVID-19 infection. Individuals were also required a minimum interval of 3 months after receipt of any immunotherapy (monoclonal antibodies, plasma) prior to the study.

A total of 765 subjects were vaccinated; 513 subjects received BIMERVAX, and 252 subjects received the COVID-19 mRNA vaccine (tozinameran). A total of 751 subjects were analysed (504 BIMERVAX subjects and 247 COVID-19 mRNA vaccine subjects) excluding those who tested positive for COVID-19 within 14 days of the booster. Randomisation was stratified by age group (18-64 versus ≥ 65 years). The median age was 42 years (range: 19 to 76 years), with similar age ranges in both vaccine arms, including 7.4% and 7.1% of subjects 65 years of age and older in the BIMERVAX and COVID-19 mRNA vaccine groups, respectively.
Immunogenicity of a booster dose of BIMERVAX was based on an assessment of geometric mean titres (GMT) of neutralising antibodies, measured by a pseudovirion-based neutralisation assay (PBNA) against SARS-CoV-2 (D614G) strain, Beta, Delta and Omicron BA.1 variants. GMT ratio is the result of the GMT values (ID_{50}) of COVID-19 mRNA vaccine (tozinameran)/BIMERVAX. Non-inferiority of BIMERVAX to COVID-19 mRNA vaccine (tozinameran) is concluded if the upper limit of the 2 sided 95% Confidence Interval (CI) of the GMT ratio is < 1.4. Superiority of BIMERVAX to COVID-19 mRNA vaccine (tozinameran) is concluded if the upper limit of the 2-sided 95% Confidence Interval of the GMT ratio is < 1.0 (see Table 2, GMT ratio column).

Table 2: Post-booster GMT ratio for BIMERVAX versus COVID-19 mRNA vaccine (tozinameran) with neutralisation titres (PBNA) against SARS-CoV-2 (D614G strain), Beta, Delta and Omicron BA.1 at days 14, 28, 98 and 182 post-booster dose (per protocol population)

	BIMERVAX N=504		**COVID-19 mRNA vaccine (tozinameran) N=247**		**COVID-19 mRNA vaccine (tozinameran) / BIMERVAX**
	GMT	95% CI	GMT	95% CI	GMT Ratio; (95% CI)
Day 14 post-booster					

D614G strain	1953.89	1667.17; 2289.93	3336.54	2778.56; 4006.57	1.71 (1.45; 2.02)
Beta	4278.92	3673.99; 4983.46	2659.02	2213.05; 3194.86	0.62 (0.52; 0.75)
Delta	1466.65	1250.52; 1720.14	1490.42	1238.77; 1793.19	1.02 (0.86; 1.21)
Omicron BA.1	2042.36	1775.91; 2348.79	1217.90	1023.84; 1448.75	0.60 (0.50; 0.72)
Day 28 post-booster					
D614G strain	2230.95	1903.29; 2615.01	2958.40	2465.00; 3550.55	1.33 (1.12; 1.56)
Beta	3774.87	3240.63; 4397.18	2467.06	2054.58; 2962.35	0.65 (0.54; 0.79)
Delta	1711.24	1458.85; 2007.29	1515.79	1260.56; 1822.71	0.89 (0.75; 1.05)
Omicron BA.1	1515.40	1317.43; 1743.13	996.73	838.49; 1184.83	0.66 (0.55; 0.79)
Day 98 post-booster (N: BIMERVAX: 78; N: tozinameran: 42 as per protocol subset)					
D614G strain	1193.35	921.24; 1545.85	1048.32	750.90; 1463.54	0.88 (0.60; 1.29)
Beta	2051.21	1571.51; 2677.34	1179.68	831.77; 1673.11	0.58 (0.38; 087)
Delta	2089.64	1609.52; 2712.99	1093.64	780.28; 1532.87	0.52 (0.35; 0.77)
Omicron BA.1	658.87	506.16; 857.66	395.69	279.04; 561.10	0.60 (0.40; 0.91)
Day 182 post-booster					
D614G strain	1205.49	1028.22; 1413.33	751.64	626.02; 902.46	0.62 (0.53; 0.74)
Beta	2569.17	2204.98; 2993.52	1786.38	1487.00; 2146.03	0.70 (0.58; 0.84)
Delta	2303.74	1963.44; 2703.03	1257.77	1045.54; 1513.07	0.55 (0.46; 0.65)
Omicron BA.1	882.92	767.34; 1015.91	668.32	561.92; 794.85	0.76 (0.63; 0.91)

N: number of participants in the population per-protocol.
Abbreviations: GMT = Geometric Mean Titre; CI: Confidence intervals; PBNA = pseudovirion-based neutralisation assay
Non-inferiority of BIMERVAX to COVID-19 mRNA vaccine (tozinameran) is concluded if the upper limit of the 2-sided 95% Confidence Interval (CI) of the GMT ratio COVID-19 mRNA vaccine (tozinameran)/BIMERVAX is < 1.4.
Superiority of BIMERVAX to COVID-19 mRNA vaccine (tozinameran) is concluded if the upper limit of the 2-sided 95% Confidence Interval of the GMT ratio COVID-19 mRNA vaccine (tozinameran)/BIMERVAX is < 1.0.

HIPRA-HH-5

This study is an ongoing open label, single arm, multicentre, phase 3 clinical trial to assess the safety and immunogenicity of a booster vaccination with BIMERVAX for the prevention of COVID-19 in subjects vaccinated with several primary vaccine schedules, with or without previous non-severe COVID-19 infections. BIMERVAX was administered at least 91 days after the last dose or at least 30 days after the COVID-19 infection. This phase 3 clinical trial excluded individuals who were pregnant as well as individuals who were immunocompromised or had received immunosuppressants within 12 weeks. Individuals were also required a minimum interval of 3 months after receipt of any immunotherapy (monoclonal antibodies, plasma) prior to the study.

The interim report includes data from a total of 2 646 subjects who were vaccinated with BIMERVAX as a booster dose in healthy individuals (at least 16 years old) previously vaccinated with different COVID-19 vaccines (mRNA COVID-19 vaccines: tozinameran and elasomeran, and adenovirus-vector vaccines (COVID-19 Vaccine (ChAdOx1-S [recombinant]) and COVID-19 vaccine (Ad26.COV2-S [recombinant]). Of these, 230 (8%) subjects were included in the immunogenicity population. In the immunogenicity analysis, the population of the Comirnaty/Comirnaty vaccine group were all subjects between 16-17 years old.

Overall, the median age was 34.4 years (range: 16 to 85 years of age). Subjects were balanced between genders, 52.49% male and 47.47% female.

Immunogenicity was measured by Pseudovirion-based neutralisation assay (PBNA) against SARS-CoV-2 (D614G) strain and against Beta, Delta and Omicron BA.1. Data on GMT (geometric mean titre: ID_{50}) at baseline (prior to the administration of the booster dose) and at Day 14 (2 weeks after the administration of the booster dose) are provided in the following table.

Table 3: Neutralising antibody Geometric Mean Titres (GMT) at 14 days post-booster with BIMERVAX in individuals 16 years of age and older-per protocol analysis

	mRNA primed (tozinameran) 16-17 years old N=11		**Ad-vector primed (ChAd=x1-S recombinant) ≥ 18 years old N=40**		**mRNA primed (elasomeran) ≥ 18 years old N=171**	
	Pre-booster					
	GMT	95% CI	GMT	95% CI	GMT	95% CI
D614G strain	720.10	356.96; 1452.64	288.58	194.56; 428.02	657.49	499.52; 865.43
Beta	471.68	208.39; 1067.60	539.49	345.97; 841.26	497.77	376.98; 657.26
Delta	803.84	376.27; 1717.26	283.75	182.43; 441.35	914.68	657.97; 1271.55
Omicron BA.1	257.99	99.98; 665.71	159.34	94.02; 270.05	221.62	155.51; 315.84
	Day 14 post-booster					
D614G strain	4753.65	2356.45; 9589.48	2298.81	1549.89; 3409.63	4437.27	3371.158; 5840.55
Beta	8820.74	3897.14; 19964.72	5009.47	3212.53; 7811.54	6857.95	5193.76; 9055.38
Delta	7564.79	3541.05; 16160.76	2600.31	1671.78; 4044.56	5811.47	4180.44; 8078.87
Omicron BA.1	5757.43	2231.25; 14856.19	1847.41	1090.05; 3131.00	4379.81	3073.24; 6241.85

N: Number of participants with available data for the relevant endpoint
Abbreviations: GMT = Geometric Mean Titre; CI: Confidence intervals

Elderly population

The immunogenicity of BIMERVAX has been shown in the elderly population (≥ 65 years old) including 38 (7.4%) of individuals receiving BIMERVAX.

Paediatric population

The European medicines Agency has deferred the obligation to submit the results of studies with BIMERVAX in one or more subsets of the paediatric population in the prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

Genotoxicity and carcinogenicity

BIMERVAX has not been evaluated for its genotoxic or carcinogenic potential. The components of the vaccine are not expected to have genotoxic or carcinogenic potential.

Reproductive toxicity

A developmental and reproductive toxicity study was performed in female and male rats prior to mating and during gestation. BIMERVAX was administered intramuscularly (equivalent to a full human dose) to female rats in four occasions, 21 and 14 days prior to mating and on gestation days 9 and 19. Males received three administrations, 35, 28 and 6 days prior to mating. No vaccine-related adverse effects on fertility, pregnancy/lactation, or development of the embryo/foetus and offspring were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dodecahydrate
Potassium dihydrogen phosphate
Sodium chloride
Potassium chloride
Water for injections

For adjuvant, see section 2

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or diluted.

6.3 Shelf life

Unopened vial

15 months at 2 ºC – 8 ºC.

Punctured vial

Chemical and physical in-use stability has been demonstrated for 6 hours at 2 ºC – 8 ºC from the time of first needle puncture.

From a microbiological point of view, after first opening (first needle puncture), the vaccine should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.

Keep the vials in the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 mL of emulsion in a multidose vial (type I glass) closed with a type I elastomeric stopper and an aluminium seal fitted with a plastic flip-off cap.

Each vial contains: 10 doses of 0.5 mL

Pack size: 10 multidose vials.

6.6 Special precautions for disposal and other handling

Handling instructions and administration

The vaccine should be handled by a healthcare professional using aseptic technique to ensure the sterility of each dose.

Preparation for use
- The vaccine comes ready to use.
- Unopened vaccine should be stored at 2 ºC to 8 ºC and kept within the outer carton to protect from light.
- Immediately prior to use, remove the vaccine vial from the outer carton.
- After first puncture of the vial, record the discard date and time (6 hours after first puncture) on the designated area of the vial label.

Inspect the vial
- Gently swirl the multidose vial before and in between each dose withdrawal. Do not shake.
- Each multidose vial contains a white and homogeneous emulsion.
- Visually inspect the vaccine for particulate matter and/or discolouration prior to administration. Do not administer the vaccine if any of these are present.

Administer the vaccine
- An overfill is included in each vial to ensure that a maximum of 10 doses of 0.5 mL each can be extracted. Discard any remaining vaccine in the vial after 10 doses have been extracted.
- Each 0.5 mL dose is withdrawn into a sterile needle and sterile syringe to be administered by intramuscular injection, preferably in the deltoid muscle of the upper arm.
- Once the vaccine is loaded in the syringe, it is stable up to at least 6 hours either under refrigerated conditions or at room temperature (< 25 ºC).
- Do not mix the vaccine in the same syringe with any other vaccines or medicinal products.
- Do not pool excess vaccine from multiple vials.

Storage after first needle puncture
- After first puncture, store the opened vial at 2 °C to 8 °C for up to 6 hours.

Discard
Discard this vaccine if not used within 6 hours after first puncture of the vial, see section 6.3.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Hipra Human Health, S.L.U.
Avda. la Selva, 135
17170 Amer (Girona)
SPAIN

8. MARKETING AUTHORISATION NUMBER(S)

PLGB 56346/0002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31/07/2023

10. DATE OF REVISION OF THE TEXT