Summary of Product Characteristics

1. Name of the Medical Product

Drug Product **:** Gemcitabine for Injection USP 1000 mg

Generic Name **:** Gemcitabine for Injection USP 1000 mg

Strength **:** 1000 mgper Vial

2. Quality and Quantitative Composition

Each mL contains:

Gemcitabine Hydrochloride USP	
Eq. to Gemcitabine	1000 mg
Excipients	q.s.

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Sterile lyophilized powder (i.e. Cake Form) as injection for Intravenous administration after reconstitution.

4. Clinical Particulars

4.1 Therapeutic Indications

Ovarian Cancer

Gemcitabine Hydrochloride in combination with Carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.

Breast Cancer

Gemcitabine Hydrochloride in combination with Paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracycline were clinically contraindicated.

Non-Small Cell Lung Cancer

Gemcitabine Hydrochloride is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.

Pancreatic Cancer

Gemcitabine Hydrochloride is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemcitabine Hydrochloride is indicated for patients previously treated with 5-FU.

4.2 Posology and method of administration

Gemcitabine Hydrochloride is for intravenous use only. Gemcitabine Hydrochloride may be administered on an outpatient basis.

Ovarian Cancer:

Gemcitabine Hydrochloride should be administered intravenously at a dose of 1000 mg/m2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Carboplatin AUC 4 should be administered intravenously on Day 1 after Gemcitabine Hydrochloride administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients

should have an absolute granulocyte count ≥ 1500 x 106/L and a platelet count ≥ 100,000 x 106/L prior to each cycle.

Breast Cancer:

Gemcitabine Hydrochloride should be administered intravenously at a dose of 1250 mg/m2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Paclitaxel should be administered at 175 mg/m2 on Day 1 as a 3-hour intravenous infusion before Gemcitabine Hydrochloride administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients should have an absolute granulocyte count ≥ 1500 x 106/L and a platelet count ≥ 100,000 x 106/L prior to each cycle.

Non-Small Cell Lung Cancer:

Two schedules have been investigated and the optimum schedule has not been determined. With the 4-week schedule, Gemcitabine Hydrochloride should be administered intravenously at 1000 mg/m2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m2 on Day 1 after the infusion of Gemcitabine Hydrochloride. With the 3-week schedule, Gemcitabine Hydrochloride should be administered intravenously at 1250 mg/m2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at a dose of 100 mg/m2 should be administered intravenously after the infusion of Gemcitabine Hydrochloride on Day 1.

Pancreatic Cancer:

Gemcitabine Hydrochloride should be administered by intravenous infusion at a dose of 1000 mg/m2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.

Preparation and Administration Precautions:

Caution should be exercised in handling and preparing Gemcitabine Hydrochloride solutions. The use of gloves is recommended. If Gemcitabine Hydrochloride solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water. Although acute dermal irritation has not been observed in animal studies, 2 of 3 rabbits exhibited drug-related systemic toxicities (death, hypoactivity, nasal discharge, shallow breathing) due to dermal absorption.

Preparation for Intravenous Infusion Administration:

The recommended diluent for reconstitution of Gemcitabine Hydrochloride Injection USP is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for Gemcitabine Hydrochloride upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.

To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200-mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1-g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200-mg vial or 1.3 mL for the 1-g vial). The total volume upon reconstitution

will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. Prior to administration the appropriate amount of drug must be diluted with 0.9% Sodium Chloride Injection. Final concentrations may be as low as 0.1 mg/mL.

Reconstituted Gemcitabine Hydrochloride is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer.

When prepared as directed, Gemcitabine Hydrochloride solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F).

Discard unused portion. Solutions of reconstituted Gemcitabine Hydrochloride should not be refrigerated, as crystallization may occur.
The compatibility of Gemcitabine Hydrochloride with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

4.3 Contraindications

Gemcitabine Hydrochloride is contraindicated in those patients with a known hypersensitivity to the drug. To make sure you can safely use Gemcitabine, tell your doctor if you have any of these other conditions:

Kidney disease;

Liver disease; or

if you are receiving radiation treatment

FDA pregnancy category D:

Do not use gemcitabine if you are pregnant. It could harm the unborn baby. Use effective birth control, and tell your doctor if you become pregnant during treatment.

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Gemcitabine Hydrochloride, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Hepatic:

Serious hepatotoxicity, including liver failure and death, has been reported in patients receiving Gemcitabine Hydrchloride alone or in combination with other potentially hepatotoxic drugs. Gemcitabine Hydrchloride should be used with caution in patients with preexisting hepatic insufficiency as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations. Administration of Gemcitabine Hydrchloride in patients with concurrent liver metastases or a preexisting medical history of hepatitis, alcoholism, or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency

Pediatric Use:

The safety and effectiveness of Gemcitabine Hydrochloride in pediatric patients has not been established. Gemcitabine Hydrochloride was evaluated in a Phase 1 trial in pediatric patients with refractory leukemia and determined that the maximum tolerated dose was 10 mg/m2/min for 360 minutes three times weekly followed by a one-week rest period. Gemcitabine Hydrochloride was also evaluated in a Phase 2 trial in patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous leukemia (10 patients) using 10 mg/m2/min for 360 minutes three times weekly followed by a one-week rest period. Toxicities observed included bone marrow suppression, febrile neutropenia, elevation of serum transaminases, nausea, and rash/desquamation, which weresimilar to those reported in adults. No meaningful clinical activity was observed in this Phase 2 trial.

Geriatric Use:

Gemcitabine Hydrochloride clearance is affected by age. There is no evidence, however, that unusual dose adjustments are necessary in patients over 65, and in general, adverse reaction rates in the single-

agent safety database of 979 patients were similar in patients above and below 65. Grade 3/4 thrombocytopenia was more common in the elderly. In the randomized clinical trial of Gemcitabine Hydrochloride in combination with carboplatin for recurrent ovarian cancer , 125 women treated with Gemcitabine Hydrochloride plus carboplatin were < 65 years and 50 were ≥ 65 years. Similar effectiveness was observed between older and younger women. There was significantly higher Grade 3/4 neutropenia in women 65 years of age or older. Overall, there were no other substantial differences in toxicity profile of Gemcitabine Hydrochloride plus carboplatin based on age.

Renal

Hemolytic Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of Gemcitabine Hydrochloride. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been reported. The majority of the cases of renal failure leading to death were due to HUS.

Gemcitabine Hydrochloride should be used with caution in patients with preexisting renal impairment as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations.

4.4 Special Warnings and precautions for use

Nausea, vomiting, diarrhea, pain/redness at the injection site, and flu-like symptoms (e.g., fever, muscle aches) may occur. Nausea and vomiting can be severe. In some cases, drug therapy may be needed to prevent or relieve nausea and vomiting. Changes in diet and lifestyle, such as eating several small meals or limiting activity, may help lessen some of these effects. If any of these effects persist or worsen, contact your doctor or pharmacist promptly.

Temporary hair loss may occur. Normal hair growth should return after treatment has ended.

Remember that your doctor has prescribed this medication because he or she has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects.

Tell your doctor right away if you have any serious side effects, including: dizziness, fainting, mouth sores, numbness/tingling of hands/feet, swelling of ankles/feet, severe stomach/abdominal pain, easy bleeding/bruising, cough, difficulty catching your breath (shortness of breath, wheezing), unusual tiredness, fast/irregular heartbeat, change in amount of urine, dark urine, yellowing of the eyes/skin.

Get medical help right away if any of these rare but very serious side effects occur: chest pain, jaw/left arm pain, weakness on one side of the body, slurred speech, vision changes, confusion.

This medication can lower your ability to fight an infection (bone marrow depression). Notify your doctor promptly if you develop any signs of infection (e.g., high fever, chills, persistent sore throat).

An allergic reaction to this drug is unlikely, but get medical help right away if it occurs. Symptoms of a serious allergic reaction include: rash, itching/swelling (especially of the face/tongue/throat), dizziness, trouble breathing.

Before using gemcitabine, tell your doctor or pharmacist if you are allergic to it; or if you have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details.

Before using this medication, tell your doctor or pharmacist your medical history, especially of: bone marrow problems (e.g., leukopenia, thrombocytopenia, anemia), heart problems (e.g., irregular heartbeat, heart failure), kidney problems, liver problems, radiation therapy.

Do not have immunizations/vaccinations without the consent of your doctor, and avoid contact with people who have recently received oral polio vaccine.

Wash your hands well to prevent the spread of infections.

To lower the chance of getting cut, bruised or injured, use caution with sharp objects like safety razors or nail cutters, and avoid activities such as contact sports. Use a soft-bristle toothbrush to lessen the risk of bleeding gums.

This medication is not recommended for use during pregnancy. Consult your doctor for more detailsand to discuss reliable forms of birth control. It is recommended that men and women use two effective

forms of birth control (e.g., condoms and birth control pills) while taking this medication and for some time afterwards.

It is not known whether this medication passes into breast milk. Because of the potential harm to the nursing infant, breast-feeding while using this drug is not recommended. Consult your doctor before breast-feeding.

4.5 Interaction with other medicinal products and other form of interactions

When Gemcitabine Hydrochloride (1250 mg/m2 on Days 1 and 8) and cisplatin (75 mg/m2 on Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was 128 L/hr/m2 and on Day 8 was 107 L/hr/m2. The clearance of cisplatin in the same study was reported to be 3.94 mL/min/m2 with a corresponding half-life of 134 hours. Analysis of data from metastatic breast cancer patients shows that, on average, Gemcitabine Hydrochloride has little or no effect on the pharmacokinetics (clearance and half-life) of paclitaxel and paclitaxel has little or no effect on the pharmacokinetics of Gemcitabine Hydrochloride. Data from NSCLC patients demonstrate that Gemcitabine Hydrochloride and carboplatin given in combination does not alter the pharmacokinetics of Gemcitabine Hydrochloride or carboplatin compared to administration of either single-agent. However, due to wide confidence intervals and small sample size, interpatient variability may be observed.

Interaction with other medical products: There may be other drugs that can interact with gemcitabine. Tell your doctor about all medications you use. This includes prescription, over-the-counter, vitamin, and herbal products. Do not start a new medication without telling your doctor.

4.6 Pregnancy and lactation

FDA pregnancy category D: Do not use gemcitabine if you are pregnant. It could harm the unborn baby. Use effective birth control, and tell your doctor if you become pregnant during treatment.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Gemcitabine Hydrochloride, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machine

No studies on the effects on the ability to drive and use machines have been performed. However, gemcitabine has been reported to cause mild to moderate somnolence, especially in combination with alcohol consumption. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

4.8 Undesirable effects

Nausea,

Vomiting,

Diarrhea,

Pain/redness at the injection site,

and flu-like symptoms (e.g., fever, muscle aches) may occur.

Nausea and vomiting can be severe. In some cases, drug therapy may be needed to prevent or relieve nausea and vomiting. Changes in diet and lifestyle, such as eating several small meals or limiting activity, may help lessen some of these effects. If any of these effects persist or worsen, contact your doctor or pharmacist promptly.

Temporary hair loss may occur. Normal hair growth should return after treatment has ended.

Tell your doctor right away if you have any serious side effects, **including:**

Dizziness,

Fainting,

Mouth sores,

Numbness/tingling of hands/feet,

Swelling of ankles/feet, severe stomach/abdominal pain,

Easy bleeding/bruising,

Cough,

Difficulty catching your breath (shortness of breath, wheezing), unusual tiredness, fast/irregularheartbeat, change in amount of urine, dark urine, yellowing of the eyes/skin.

Get medical help right away if any of these rare but very serious side effects occur:

chest pain, Jaw/left arm pain,

Weakness on one side of the body,

Slurred speech,

Vision changes,

Confusion.

This medication can lower your ability to fight an infection (bone marrow depression). Notify your doctor promptly if you develop any signs of infection (e.g., high fever, chills, persistent sore throat).

An allergic reaction to this drug is unlikely, but get medical help right away if it occurs.

Symptoms of a serious allergic reaction include:

Rash,

Itching/swelling (especially of the face/tongue/throat),

Dizziness,

Trouble breathing.

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 EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdosage

There is no known antidote for overdoses of Gemcitabine HydrochlorideMyelosuppression, paresthesias, and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m2 was administered by intravenous infusion over 30 minutes every 2 weeks to several patients in a Phase 1 study. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

If overdose is suspected, contact your local poison control center or emergency room immediately

Brief Clinical description of Symptoms

Overdose symptoms may include numbness or tingly feeling, severe skin rash, fever, chills, flu symptoms, or any signs of infection.

Tell your doctor right away if you have any serious side effects, including:

Dizziness, Fainting, Mouth sores, Numbness/tingling of hands/feet, Swelling of ankles/feet, severe stomach/abdominal pain, Easy bleeding/bruising, Cough, Difficulty catching your breath (shortness of breath, wheezing), unusual tiredness, fast/irregular heartbeat, change in amount of urine, dark urine, yellowing of the eyes/skin.

Get medical help right away if any of these rare but very serious side effects occur:

chest pain, Jaw/left arm pain, Weakness on one side of the body, Slurred speech, Vision changes, Confusion. This medication can lower your ability to fight an infection (bone marrow depression). Notify your doctor promptly if you develop any signs of infection (e.g., high fever, chills, persistent sore throat).

An allergic reaction to this drug is unlikely, but get medical help right away if it occurs.

Symptoms of a serious allergic reaction include:

Rash, Itching/swelling (especially of the face/tongue/throat), Dizziness, Trouble breathing.

Treatment of Overdosage

If for any reason an overdose of Gemcitabine Hydrochloride is suspected, seek emergency medical attention or contact your healthcare provider immediately.
There is no specific antidote. Treatment of overdosage should be symptomatic

5. Pharmacological properties

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: pyrimidine analogues (Cytotoxic)

ATC code: L01BC05

Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin in vitro.No effect of cisplatin on gemcitabine triphosphate accumulation or DNA double-strand breaks was observed. In vivo, gemcitabine showed activity in combination with cisplatin against the LX-1 and CALU-6 human lung xenografts, but minimal activity was seen with the NCI-H460 or NCI-H520 xenografts. Gemcitabine was synergistic with cisplatin in the Lewis lung murine xenograft. Sequential exposure to gemcitabine 4 hours before cisplatin produced the greatest interaction

5.2 Pharmacokinetics Properties

Absorption and Distribution

The pharmacokinetics of gemcitabine were examined in 353 patients, with various solid tumors. Pharmacokirietic parameters were derived using data from patients treated for varying durations of therapy given weekly with periodic rest weeks and using both short infusions (< 70 minutes) and long infusions (70 to 285 minutes). The total Gemitabine Hydrochloride dose varied from 500 to 3600 mg/m2.

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m2 following infusions lasting < 70 minutes. For long infusions, the volume of distribution rose to 370 L/m2.

Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Gemcitabine plasma protein binding is negligible.

Metabolism

Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/m2/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (< 10%) and the inactive uracil metabolite, 2'-deoxy-2',2'-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma.

The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

Excretion

Clearance of gemcitabine was affected by age and gender. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion resultin changes in half-life and plasma concentrations.

5.3 Preclinical safety data

Ovarian Cancer

The safety and efficacy of Gemcitabine was studied in a randomized trial of 356 women with advanced ovarian cancer that had relapsed at least 6 months after first-line platinum-based therapy. Patients were randomized to receive either Gemcitabine 1000 mg/m² on Days 1 and 8 of a 21-day cycle and carboplatin AUC 4 administered after Gemcitabine infusion on Day 1 of each cycle (n=178) or to carboplatin AUC 5 administered on Day 1 of each 21-day cycle (n=178). The primary efficacy outcome measure was progression free survival (PFS).

Breast Cancer

The safety and efficacy of Gemcitabine were evaluated in a multi-national, randomized, open-label trial conducted in women receiving initial treatment for metastatic breast cancer in women who have received prior adjuvant/neoadjuvant anthracycline chemotherapy unless clinically contraindicated. Patients were randomized to receive Gemcitabine 1250 mg/m² on Days 1 and 8 of a 21-day cycle and paclitaxel 175 mg/m² administered prior to Gemzar on Day 1 of each cycle (n=267) or to receive paclitaxel 175 mg/m² was administered on Day 1 of each 21-day cycle (n=262). The primary efficacy outcome measure was time to documented disease progression.

A total of 529 patients were enrolled; 267 were randomized to Gemcitabine and paclitaxel and 262 to paclitaxel alone. Demographic and baseline characteristics were similar between treatment arms. The addition of Gemcitabine to paclitaxel resulted in statistically significant improvement in time to documented disease progression and overall response rate compared to paclitaxel alone. There was no significant difference in overall survival.

6. Pharmaceutical Particulars

6.1 List of excipients

Following excipients used during the manufacturing of Gemcitabine For Injection USP

Mannitol USP as bulking agent

Sodium Acetate USP as buffering agent

Water for Injection USP as vehicle.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal product except sodium chloride 9 mg/mL (0.9%) solution

6.3 Shelf life

24 months from date of manufacturing

6.4 Special precautions for storage

From microbiological point of view reconstituted solution should be used immediately. Do not store the reconstituted solution in refrigerator as crystallization may occur.

Store at a temperature not exceeding 25º (77º F), excursion permitted between 15 º and 30º (59º and 86º F).

6.5. Nature and contents of container

50 mL Clear Glass Vial USP Type I

20 mm Bromo butyl rubber plug

20 mm Aluminium flip off seal

6.6 Special precautions for disposal and other handling

Handling

The normal safety precautions for cytostatic agents must be observed when preparing and disposing of the infusion solution. Handling of the solution for infusion should be done in a safety box and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented

with a mask and protective glasses. If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should be rinsed immediately and thoroughly with water. Ifthere is lasting irritation, a doctor should be consulted. If the solution is spilled on the skin, rinse thoroughly with water. Instructions for reconstitution (and further dilution, if performed). The only approved diluent for reconstitution of gemcitabine sterile powder is sodium chloride 9 mg/mL (0.9%) solution for injection (without preservative). Due to solubility considerations, the maximum concentration for gemcitabine upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution and should be avoided.

1. Use aseptic technique during the reconstitution and any further dilution of gemcitabine for intravenous infusion administration.

2. To reconstitute, add 5 mL of sterile sodium chloride 9 mg/mL (0.9 %) solution for injection, without preservative, to the 200 mg vial or 25 mL sterile sodium chloride 9 mg/mL (0.9 %) solution for injection, without preservative, to the 1 g vial. This yields a gemcitabine concentration of 38 mg/mL, which includes accounting for the displacement volume of the lyophilized powder. Shake to dissolve. Further dilution with sterile sodium chloride 9 mg/mL (0.9 %) solution for injection, without preservative can be done. Reconstituted solution is a clear colourless solution.

3. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

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

7. Marketing authorisation holder

Beta Drugs Limited
Kharuni-Lodhimajra Road,
Vill: Nandpur, Baddi, Distt. Solan,
Himachal Pradesh, 173205 INDIA

8. Marketing authorisation number(s)

07492/08885/NMR/2021

9. Date of first authorisation

02 Jun 2022

10. Date of revision of the text

July 2024