SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

GEMLIFE 200mg (Gemcitabine 200mg lyophilized powder for injection.)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains gemcitabine hydrochloride eq to 200mg gemcitabine.

Excipient(s) with known effect:

Each ml contains 200mg mannitol.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Lyophilized powder for Injection

White lyophilized cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- **Non-Small Cell Lung Cancer:**

  Gemcitabine, alone for elderly patients or for palliative treatment, or in combination with cisplatin, is indicated for the first line treatment of patients with locally advanced or metastatic non small cell lung cancer.

- **Pancreatic Cancer:**

  Gemcitabine is indicated for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas. Gemcitabine is indicated for patients with 5-FU refractory pancreatic cancer. Patients treated with gemcitabine may derive improvement in survival, significant clinical benefit, or both.

  Gemcitabine is an option for first-line chemotherapy for patient with advanced or metastatic adenocarcinoma of the pancreas and a karnofsky score of at least 50 (Karnofsky score is a measure of the ability to perform ordinary tasks).

- **Bladder Cancer:**

  Gemcitabine in combination with cisplatin is indicated for the treatment of patients with bladder cancer.

- **Breast Cancer:**

  Gemcitabine, in combination with paclitaxel, is indicated for the first line treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following

adjuvant/neoadjuvant chemotherapy, containing anthracycline, unless clinically contraindicated. Gemcitabine in combination with paclitaxel, is an option for the treatment of metastatic breast cancer only when docetaxelmonotherapy or docetaxel plus capecitabine are also considered appropriate.

- **Ovarian Cancer:**

  Gemcitabine, in combination with carboplatin, is indicated for the treatment of patients with locally advanced or metastatic epithelial ovarian cancer which has relapsed after a recurrence free interval of at least 6 months following previous platinum based therapy.

4.2 Posology and method of administration

Gemcitabine is for intravenous use only.

Non-Small Cell Lung Cancer: As per literature reports, with the 4-week schedule, Gemcitabine should be administered intravenously at 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m^2 on Day1 after the infusion of Gemcitabine. With the 3-week schedule, Gemcitabine should be administered intravenously at 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at a dose of 100 mg/m^2 should be administered intravenously after the infusion of Gemcitabine on Day 1.

Dose Modifications: Dosage adjustments for hematologic toxicity may be required for Gemcitabine and for Cisplatin. Gemcitabine dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients receiving Gemcitabine should be monitored prior to each dose with a complete blood count (CSC), including differential and platelet counts. If marrow suppression is detected, therapy should be modified or suspended. In general, for severe (Grade 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with Gemcitabine plus Cisplatin should be held or decreased by 50% depending on the judgment of the treating physician. During combination therapy with Cisplatin, serum creatinine, serum potassium, serum calcium, and serum magnesium should be carefully monitored (Grade 3/4 serum creatinine toxicity for Gemcitabine plus Cisplatin was 5% versus 2% for Cisplatin alone).

Pancreatic Cancer: Gemcitabine should be administered by intravenous infusion at a dose of 1000 mg/m^2 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.

Dose Modifications: Dosage adjustment is based upon the degree of hematologic toxicity experienced by the patient. Clearance in women and the elderly is reduced and women were somewhat less able to progress to subsequent cycles. Patients receiving Gemcitabine should be monitored prior to each dose

with a complete blood count (CSC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 1.

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
≥100	And	>100,000	100
500-999	Or	50,000-99,999	75
<500	Or	<50,000	Hold

Laboratory evaluation of renal and hepatic function, including transaminases and serum creatinine, should be performed prior to initiation of therapy and periodically thereafter. Gemcitabine should be administered with caution in patients with evidence of significant renal or hepatic impairment as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations.

Patients treated with Gemcitabine who complete an entire cycle of therapy may have the dose for subsequent cycles increased by 25%, provided that the absolute granulocyte count (AGC) and platelet nadirs exceed 1500 x 10^6/L and 100,000 x 10^6/L, respectively, and if non-hematologic toxicity has not been greater than WHO Grade 1. If patients tolerate the subsequent course of Gemcitabine at the increased dose, the dose for the next cycle can be further increased by 20%, provided again that the AGC and platelet nadirs exceed 1500 x 10^6/L and 100,000 x 10^6/L, respectively, and that non-hematologic toxicity has not been greater than WHO Grade 1.

Bladder Cancer, At the Invasive Stage: The recommended dose of Gemcitabine in combination with cisplatin, is 1,000 mg/m^2, given by 30 minutes intravenous infusion on Days 1, 8 and 15, followed by one-week rest period for a 28-day cycle. Cisplatin is given at a recommended dose of 70 mg/m^2 on day 2. This four-week cycle is then repeated. A dosage reduction or delay before each administration of the chemotherapy may be applied, based upon the amount of toxicity experienced by the patient. A clinical trial showed more myelosuppression when cisplatin was used in doses of 100 mg/m^2.

Breast Cancer _ Gemcitabine should be administered intravenously at a dose of 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Paclitaxel should be administered at 175 mg/m^2 on Day 1 as a 3-hour intravenous infusion before Gemcitabine 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 10^6/L and a platelet count ≥100,000 x 10^6/L prior to each cycle.

Dose Modifications: Gemcitabine dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on Day 8 of therapy. If marrow suppression is detected, Gemcitabine dosage should be modified according to the guidelines in Table 2.

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
≥1200	And	>75,000	100
1000-1199	Or	50,000-75,000	75
700-999	And	≥ 50,000	50
<700	Or	<50,000	Hold

In general, for severe (Grade 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with Gemcitabine should be held or decreased by 50% depending on the judgment of the treating physician.

Ovarian Cancer Gemcitabine should be administered intravenously at a dose of 1000 mg/m^2 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 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 10^6/L and a platelet count ≥100,000 x 10^6/L prior to each cycle.

Dose Modifications: Gemcitabine dosage adjustment for hematological toxicity within a cycle of treatment is based on the granulocyte and platelet counts taken on Day 8 of therapy. If marrow suppression is detected, Gemcitabine dosage should be modified according to guidelines in Table 3.

Table 3: Day 8 Dosage Reduction Guidelines for Gemcitabine in Combination with Carboplatin Contraindications:

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
≥1500	And	≥100,000	100
1000-1499	And/or	75,000-99,999	50
<1000	And/or	<75,000	Hold

In general, for severe (Grade 3 or 4) non-hematological toxicity, except nausea/vomiting, therapy with Gemcitabine should be held or decreased by 50% depending on the judgment of the treating physician.

Dose adjustment for Gemcitabine in combination with carboplatin for subsequent cycles is based upon observed toxicity. The dose of Gemcitabine in subsequent cycles should be reduced to 800 mg/m^2 on Days 1 and 8 in case of any of the following hematologic toxicities:

Absolute granulocyte count <500 x 10^6/L for more than 5 days

Absolute granulocyte count <100 x 10^6/L for more than 3 days

Febrile neutropenia

Platelets <25,000 x 10^6/L

Cycle delay of more than one week due to toxicity

If any of the above toxicities recur after the initial dose reduction, for the subsequent cycle, Gemcitabine should be given on Day 1 only at 800 mg/m^2.

Preparation and Administration Precautions: Caution should be exercised in handling and preparing Gemcitabine solutions. The use of gloves is recommended. If Gemcitabine solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water. Procedures for proper handling and disposal of anti-cancer drugs should be considered.

Preparation for Intravenous Infusion Administration: The recommended diluent for reconstitution of Gemcitabine is 0.9% Sodium Chloride 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.

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 l-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 l-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 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 permits. If particulate matter or discoloration is found, do not administer. When prepared as directed, Gemcitabine solutions are stable for 24 hours at controlled room temperature of 20° to 25°C. Discard unused portion. Solutions of reconstituted Gemcitabine should not be refrigerated, as crystallization may occur. The compatibility of Gemcitabine 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 is contraindicated in those patients with a known hypersensitivity to the medicine or any of the excipients in the medicinal product.

4.4 Special warnings and precautions for use

Prolongation of the infusion time and increased dosing frequency has been shown to increase toxicity.

Gemcitabine can suppress bone marrow function as manifested by leucopoenia, thrombocytopenia and anemia. However, myelosuppression is short-lived and usually does not result in dose reductions and rarely in discontinuation.

Precautions

General

Patients receiving therapy with gemcitabine must be monitored closely. Laboratory facilities should be available to monitor patient status. Treatment for a patient compromised by medicine toxicity may be required.

Schedule-dependent Toxicity

As per clinical trial reports evaluating the maximum tolerated dose of gemcitabine, prolongation of the infusion time beyond 60 minutes or more frequent than weekly dosing resulted in an increased incidence of clinically significant hypotension, severe flu-like symptoms, myelosuppression, and asthenia. The half-life of Gemcitabine for injection is influenced by the length of the infusion.

Myelosuppression

Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with Gemcitabine as a single agent and the risks are increased when Gemcitabine is combined with other cytotoxic drugs.

Pulmonary Toxicity and Respiratory Failure

As per reported clinical trials, pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported. In some cases, these pulmonary events can lead to fatal respiratory failure despite discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks after the last dose of Gemcitabine. Discontinue Gemcitabine in patients who develop unexplained dyspnea, with or without bronchospasm, or have any evidence of pulmonary toxicity

Hemolytic Uremic Syndrome

Hemolytic uremic syndrome, including fatalities from renal failure or the requirement for dialysis can occur in patients treated with Gemcitabine. Assess renal function prior to initiation of Gemcitabine and periodically during treatment. Consider the diagnosis of HUS in patients who develop anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, or reticulocytosis; severe thrombocytopenia; or evidence of renal failure (elevation of serum creatinine or BUN). Permanently discontinue Gemcitabine in patients with HUS or severe renal impairment. Renal failure may not be reversible even with discontinuation of therapy.

Hepatic Toxicity

Drug-induced liver injury, including liver failure and death, has been reported in patients receiving Gemcitabine alone or in combination with other potentially hepatotoxic drugs. Administration of Gemcitabine in patients with concurrent liver metastases or a pre-existing medical history or hepatitis,

alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency. Assess hepatic function prior to initiation of Gemcitabine and periodically during treatment. Discontinue Gemcitabine in patients that develop severe liver injury.

Embryofetal Toxicity

Gemcitabine can cause fetal harm when administered to a pregnant woman, based on its mechanism of action. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits. If this drug is used during pregnancy, or if a woman becomes pregnant while taking Gemcitabine, the patient should be apprised of the potential hazard to a fetus

Exacerbation of Radiation Therapy Toxicity

Gemcitabine is not indicated for use in combination with radiation therapy.

Concurrent (given together or ≤7 days apart) – Life-threatening mucositis, especially esophagitis and pneumonitis occurred in a trial in which Gemcitabine was administered at a dose of 1,000 mg/m^2 to patients with non-small cell lung cancer for up to 6 consecutive weeks concurrently with thoracic radiation.

Non-concurrent (given >7 days apart) – Excessive toxicity has not been observed when Gemcitabine is administered more than 7 days before or after radiation. Radiation recall has been reported in patients who receive Gemcitabine after prior radiation.

Capillary Leak Syndrome

Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving Gemcitabine as a single agent or in combination with other chemotherapeutic agents. Discontinue Gemcitabine if CLS develops during therapy.

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving Gemcitabine as a single agent or in combination with other chemotherapeutic agents. PRES can present with headache, seizure, lethargy, hypertension, confusion, blindness, and other visual and neurologic disturbances. Confirm the diagnosis of PRES with magnetic resonance imaging (MRI) and discontinue Gemcitabine if PRES develops during therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term duration animal studies have not been conducted to evaluate the carcinogenic potential of gemcitabine. Cytogenetic damage has been produced by gemcitabine in an in vivo assay.

Gemcitabine induced forward mutation in vitro in a mouse lymphoma assay. Gemcitabine causes a reversible, dose- and schedule-dependent hypospermatogenesis in male mice. Although animal studies have shown an effect of gemcitabine on male fertility, no effect has been demonstrated on female fertility.

4.5 Interaction with other FPP's and other forms of Interaction

Radiotherapy

Concurrent (given together or less than or equal to 7 days apart)

Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Pre-clinical and clinical studies have shown that gemcitabine has radiosensitising activity.

In a single trial, where gemcitabine at a dose of 1000 mg/m^2 was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe, and potentially life threatening mucositis, especially esophagitis, and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy (median treatment volumes 4795 cm^3). Studies done subsequently have suggested that it is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as a phase II study in non-small cell lung cancer. Thoracic radiation doses of 66Gy were administered with gemcitabine (600 mg/m^2, four times) and cisplatin (80 mg/m^2, twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined in all tumor types.

Radiation injury has been reported on targeted tissues (e.g. oesophagitis, colitis, and pneumonitis) in association with both concurrent and non-concurrent use of gemcitabine.

Sequential (given >7 days apart)

Available information does not indicate any enhanced toxicity with administration of gemcitabine in patients who received prior radiation, other than radiation recall. Data suggest that gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiation. Available information does not indicate any enhanced toxicity from radiation therapy following gemcitabine exposure.

4.6 Pregnancy and lactation

Pregnancy

Category D Because of the potential for abnormalities with cytotoxic therapy, particularly during the first trimester, gemcitabine must not be used during pregnancy. Studies in experimental animals (mice and rabbits at doses up to 4.5 and 1.6 mg/m^2/day IV respectively, administered during the period of organogenesis) have shown teratogenicity and embryo toxicity. Peri- and postnatal studies in mice at doses up to 4.5 mg/m^2/day have shown retarded physical development in the offspring. Women of childbearing age receiving gemcitabine should be advised to avoid becoming pregnant, and to inform

the treating physician immediately should this occur. Men must avoid fathering a child during and for 6 months after treatment.

Lactation

It is not known whether gemcitabine is excreted in human milk, however, studies in lactating rats have shown gemcitabine and/or its metabolites in the milk 10 minutes after an IV dose to the dam. Brest feeding should be discontinued by nursing women because of the potential hazard to the infant.

Usage in Children

Gemcitabine has not been studied in children.

4.7 Effects on ability to drive and use machines

Gemcitabine has been reported to cause mild to moderate somnolence. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

4.8 Undesirable effects

The following serious adverse reactions are discussed in greater detail in warnings & Precautions sections:

Schedule-dependent Toxicity

Myleosuppression

Pulmonary Toxicity and Respiratory Failure

Hemolytic Uremic Syndrome

Hepatic Toxicity

Embryofetal Toxicity

Exacerbation of Radiation Toxicity

Capillary Leak Syndrome

Posterior Reversible Encephalopathy Sydrome

4.9 Overdose

There is no antidote for overdosage of Gemcitabine. Single doses as high as 5.7 g/m^2 have been administered by IV infusion over 30 minutes every 2 weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pyrimidine analogues

ATC code: L01BC05

Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate and triphosphate nucleosides. The cytotoxic action of gemcitabine appears to be due to inhibition of DNA synthesis by two actions of active diphosphate and triphosphate. First, diphosphate inhibits ribonucleotidereductase, which is uniquely responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by triphosphate causes a reduction in the concentrations of deoxynucleosides. Likewise, a small amount of gemcitabine may also be incorporated into RNA. DNA polymerase epsilon is essentially unable to remove gemcitabine and repair the growing DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition, there is essentially a complete inhibition in further DNA synthesis (masked chain termination). After incorporation into DNA, gemcitabine then appears to induce the programmed cellular death process known as apoptosis.

5.2 Pharmacokinetic properties

The pharmacokinetics of gemcitabine have been examined in 353 patients in seven studies. The 121 women and 232 men ranged in age from 29 to 79 years. Of these patients, approximately 45% had non-small cell lung cancer and 35% were diagnosed with pancreatic cancer. The following pharmacokinetic parameters were obtained for doses ranging from 500 to 2,592 mg/m^2 that were infused from 0.4 to 1.2 hours.

Peak Plasma Concentrations (obtained within 5 minutes of the end of the infusion): 3.2 to 45.5 mcg/ml.

Volume of Distribution of the Central Compartment: 12.4 L/m^2 for women and 17.5 L/m^2 for men (inter-individual variability was 91.9%).

Volume of Distribution of the Peripheral Compartment: 47.4 L/m^2. The volume of the peripheral compartment was not sensitive to gender.

Plasma Protein Binding: negligible.

Systemic Clearance: Ranged from 29.2 L/hr/m^2 to 92.2 L/hr/m^2 depending on gender and age (inter-individual variability was 52.2%). Clearance for women is approximately 25% lower than the values for men. Although rapid, clearance for both men and women appears to decrease with age. For the recommended gemcitabine dose of 1000 mg/m^2 given as a 30 minute infusion, lower clearance values for women and men should not necessitate a decrease in the gemcitabine dose.

Urinary Excretion: less than 10% is excreted as unchanged drug.

Renal Clearance: 2 to 7 L/hr/m^2.

Half-Life: Ranged from 42 to 94 minutes depending on age and gender. For the recommended dosing schedule, gemcitabine elimination should be virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly.

Metabolism: Gemcitabine is rapidly metabolised by cytidine deaminase in the liver, kidney, blood and other tissues. This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells. Half-life of terminal elimination: 0.7 to 12 hours. Intracellular concentrations increase in proportion to gemcitabine doses of 35 to 350mg/m^3/30min, which give steady state concentrations of 0.4 to 5 mcg/mL. At gemcitabine plasma concentration above 5 micrograms/mL, dFdCTP levels do not increases, suggesting that the formation is saturable in these cells. Parent plasma concentrations following a dose of 1000mg/m^2/30 min are greater than 5 mcg/ml for approximately 30 minutes after the end of the infusion, and greater than 0.4 mcg/ml for an additional hour.

5.3 Preclinical safety data

In repeat-dose studies of up to 6 months in duration in mice and dogs, the principal finding was schedule and dose-dependent haematopoietic suppression which was reversible.

Gemcitabine is mutagenic in an in vitro mutation test and an in vivo bone marrow micronucleus test. Long term animal studies evaluating the carcinogenic potential have not been performed.

In fertility studies, gemcitabine caused reversible hypospermatogenesis in male mice. No effect on the fertility of females has been detected.

Evaluation of experimental animal studies has shown reproductive toxicity e.g. birth defects and other effects on the development of the embryo or foetus, the course of gestation or peri- and postnatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium Acetate

Sodium Hydroxide

Hydrochloric acid

Water for Injection.

6.2 Incompatibilities

The compatibility of Gemcitabine for Injection (Lyophilized) with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at controlled room temperature (15°C to 25°C). Keep out of reach of children. Do not refrigerate after reconstitution.

6.5 Nature and contents of container

50 ml flint moulded USP type I vial closed with 20mm grey butyl rubber plug and sealed with 20mm aluminium flip off seal. Such 1 vial is placed in a carton along with pack insert.

6.6 Instructions for use and handling

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

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

07490/08165/NMR/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

02/06/2022

10. DATE OF REVISION OF THE TEXT

18/07/2023