SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zavedos 1mg/mL Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 1 mg of idarubicin hydrochloride.

Each vial of 5 mL of solution contains 5 mg of idarubicin hydrochloride.

Each vial of 10 mL of solution contains 10 mg of idarubicin hydrochloride.

Each vial of 20 mL of solution contains 20 mg of idarubicin hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection

Orange-red, clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

For the treatment of acute myeloid leukaemia (AML), for remission induction in untreated patients or for remission induction in relapsed or refractory patients.

For second line treatment of relapsed acute lymphoblastic leukaemia (ALL).

Paediatric population

For first line treatment of acute myeloid-leukaemia (AML), in combination with cytarabine, for remission induction.

For second line treatment of relapsed acute lymphoblastic leukaemia (ALL).

Zavedos may be used in combination chemotherapy regimens involving other cytotoxic agents (see section 4.2).

4.2 Posology and method of administration

Posology

Dosage is calculated on the basis of body surface area.

Acute myeloid leukaemia (AML)

Adults
12 mg/m^2/day i.v. daily for 3 days in combination with cytarabine.
or
8 mg/m^2/day i.v. daily for 5 days with/without combination.

Paediatric population
10-12 mg/m^2/day i.v. daily for 3 days in combination with cytarabine.

Acute lymphoblastic leukaemia (ALL)

Adults
As single agent in ALL the suggested dose in adults is 12 mg/m^2/day i.v. daily for 3 days.

Paediatric population
10 mg/m^2/day i.v. daily for 3 days, as a single agent.

NOTE: These are general guidelines. Refer to individual protocols for exact dosage.

All of these dosage schedules should, however, take into account the haematological status of the patient and the dosages of other cytotoxic drugs when used in combination.

Administration of a second course should be delayed in patients who develop severe mucositis until recovery from this toxicity has occurred and a dose reduction of 25% is recommended.

Method of administration

For intravenous use only.

Not for intrathecal use.

4.3 Contraindications

- Hypersensitivity to idarubicin or to any of the excipients listed in section 6.1, other anthracyclines or anthracenediones
- Severe hepatic impairment
- Severe renal impairment
- Uncontrolled infections
- Severe cardiomyopathy
- Recent myocardial infarction
- Severe arrhythmias

- Persistent myelosuppression
- Previous treatment with maximum cumulative doses of idarubicin hydrochloride and/or other anthracyclines and anthracenediones (see section 4.4)
- Breast-feeding should be stopped during drug therapy (see section 4.6).

4.4 Special warnings and precautions for use

General
Idarubicin should be administered only under the supervision of physicians experienced in the use of cytotoxic chemotherapy.

This ensures that immediate and effective treatment of severe complications of the disease and/or its treatment (e.g. haemorrhage, overwhelming infections) may be carried out.

Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) before beginning treatment with idarubicin hydrochloride.

Haematological toxicity
Idarubicin is a potent bone marrow suppressant. Severe myelosuppression will occur in all patients given a therapeutic dose of this agent.

Haematological profiles should be assessed before and during each cycle of therapy with idarubicin, including differential white blood cell (WBC) counts.

A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of idarubicin haematologic toxicity and is the most common acute dose limiting toxicity of the drug.

Leukopenia and neutropenia are usually severe, thrombocytopenia and anaemia may also occur. Neutrophil and platelet counts usually reach their nadir 10 to 14 days after drug administration; however, cell counts generally return to normal levels during the third week.

During the phase of severe myelosuppression, deaths due to infections and/or haemorrhages have been reported.

Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death. If febrile neutropenia occurs, treatment with an i.v. antibiotic is recommended.

Secondary leukaemia
Secondary leukaemia, with or without a preleukaemic phase, has been reported in patients treated with anthracyclines, including idarubicin. Secondary leukaemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pre-treated with cytotoxic

drugs, or when doses of the anthracyclines have been escalated. These leukaemias can have a 1 to 3 year latency period.

Cardiac function

Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e. acute) or late (i.e. delayed) events.

Early (i.e. acute) events

Early cardiotoxicity of idarubicin consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities, such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not a reason for the discontinuation of idarubicin treatment.

Late (i.e. delayed) events

Delayed cardiotoxicity usually develops late in the course of therapy or within 2 to 3 months after treatment termination, but later events, several months to years after completion of treatment have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly, hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

Cumulative dose limits for i.v. or oral idarubicin hydrochloride have not been defined. However, idarubicin-related cardiomyopathy was reported in 5% of patients who received cumulative i.v. doses of 150 to 290 mg/m^2. Available data on patients treated with oral idarubicin hydrochloride total cumulative doses up to 400 mg/m^2 suggest a low probability of cardiotoxicity.

Cardiac function should be assessed before patients undergo treatment with idarubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of idarubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes Multiple Gated Acquisition (MUGA) scan or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, and concomitant use of drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g. trastuzumab). Anthracyclines including idarubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored (see section 4.5). Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The reported half-life of trastuzumab is variable. The substance may persist in circulation for up to 7 months.

Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If this is not possible, the patient's cardiac function should be monitored carefully.

Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with idarubicin may occur at lower cumulative doses whether or not cardiac risk factors are present.

In infants and children there appears to be a greater susceptibility to anthracycline induced cardiac toxicity, and a long-term periodic evaluation of cardiac function has to be performed.

It is probable that the toxicity of idarubicin and other anthracyclines or anthracenediones is additive.

Hepatic and renal function
Since hepatic and/or renal function impairment can affect the disposition of idarubicin, liver and kidney function should be evaluated with conventional clinical laboratory tests (using serum bilirubin and serum creatinine as indicators) prior to, and during, treatment. In a number of Phase III clinical trials, treatment was contraindicated if bilirubin and/or creatinine serum levels exceeded 2.0 mg %. With other anthracyclines a 50% dose reduction is generally used if bilirubin levels are in the range 1.2-2.0 mg %.

Gastrointestinal
Idarubicin is emetogenic. Mucositis (mainly stomatitis, less often oesophagitis) generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

Occasionally, episodes of serious gastrointestinal events (such as perforation or bleeding) have been observed in patients receiving oral idarubicin who had acute leukaemia or a history of other pathologies or had received medications known to lead to gastrointestinal complications. In patients with active gastrointestinal disease with increased risk of bleeding and/or perforation, the physician must balance the benefit of oral idarubicin therapy against the risk.

Effects at site of injection
Phlebosclerosis may result from an injection into a small vessel or from previous injections into the same vein. Following the recommended administration procedures may minimise the risk of phlebitis/thrombophlebitis at the injection site.

Extravasation
Extravasation of idarubicin during intravenous injection may cause local pain, severe tissue lesions (vesication, severe cellulitis), and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of idarubicin, the drug infusion should be immediately stopped.

In cases of extravasation dexrazoxane can be used to prevent or reduce tissue injury.

Tumour lysis syndrome
Idarubicin may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies rapid drug-induced lysis of neoplastic cells ('tumour lysis syndrome'). Blood uric acid levels, potassium, calcium phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalinisation,

and prophylaxis with allopurinol to prevent hyperuricaemia may minimize potential complications of tumour lysis syndrome.

Immunosuppressant effects/increased susceptibility to infections
Administration of live or live-attenuated vaccines (like yellow fever) in patients immunocompromised by chemotherapeutic agents including idarubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving idarubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Reproductive system
Idarubicin can cause genotoxicity. Male and female patients treated with idarubicin hydrochloride are advised to adopt effective contraceptive measures during therapy and for a period after treatment.
Men treated with idarubicin hydrochloride are advised, if appropriate and available, to seek advice on sperm preservation due to the possibility of irreversible infertility caused by the therapy (see section 4.6). Patients desiring to have children after completion of therapy should be advised to discuss with an appropriate specialist first.

Other
As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism have been coincidentally reported with the use of idarubicin.

The product may cause a red colouration of the urine for 1-2 days after administration and patients should be advised of this fact.

4.5 Interaction with other medicinal products and other forms of interaction

Idarubicin is a potent myelosuppressant and combination chemotherapy regimens including other agents with similar action may be expected to induce additive myelosuppressive effects (see section 4.4).

Changes in hepatic or renal function induced by concomitant therapies may affect idarubicin metabolism, pharmacokinetics and therapeutic efficacy and/ or toxicity (see section 4.4).

The use of idarubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blockers), requires monitoring of cardiac function throughout treatment. An additive myelosuppressant effect may occur when radiotherapy is given concomitantly or within 2-3 weeks prior to treatment with idarubicin.

Concomitant use of live attenuated vaccines (e.g. yellow fever) is not recommended, due to a risk of possibly fatal systemic disease. The risk is increased in subjects who are already immunosuppressed by their underlying disease. An inactivated vaccine should be used if available.

At combination of oral anticoagulants and anticancer chemotherapy, increased frequency of the INR (International Normalised Ratio) monitoring is recommended, since the risk for an interaction cannot be excluded.

Cyclosporin A: The co-administration of cyclosporin A as a single chemosensitizer significantly increased idarubicin AUC (1.78-fold) and idarubicinol AUC (2.46-fold)

in patients with acute leukaemia. The clinical significance of this interaction is unknown. A dosage adjustment may be necessary in some patients.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited amount of data from the use of idarubicin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Idarubicin should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus. The patient should be informed of the potential hazard to the foetus.

Women of childbearing potential / Contraception in males and females
Women of childbearing potential should be advised not to become pregnant and to use effective contraception during treatment with idarubicin and for at least 6.5 months after the last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with idarubicin and for at least 3.5 months after the last dose (see section 4.4).

Breast-feeding
It is not known whether idarubicin or its metabolites are excreted in human milk. As other anthracyclines are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from idarubicin, women should be advised not to breastfeed during treatment with idarubicin and for at least 14 days after the last dose.

Fertility
Idarubicin can induce chromosomal damage in human spermatozoa. Both men and women should seek advice on fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

The effect of idarubicin on the ability to drive or use machinery has not been systematically evaluated.

4.8 Undesirable effects

The frequencies of undesirable effects are based on the following categories:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (frequency cannot be estimated from the available data)

Infections and infestations	
Very common	Infections
Uncommon	Sepsis, septicaemia
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Secondary leukaemia (acute myeloid leukaemia and myelodysplastic syndrome)
Blood and lymphatic system disorders	
Very common	Anaemia, severe leukopenia and neutropenia, thrombocytopenia
Not known	Pancytopenia
Immune system disorders	
Very rare	Anaphylaxis
Endocrine disorders	
Very common	Anorexia
Uncommon	Dehydration
Metabolism and nutrition disorders	
Uncommon	Hyperuricaemia
Not known	Tumour Lysis Syndrome
Nervous system disorders	
Rare	Cerebral haemorrhages
Cardiac disorders	
Common	Bradycardia, sinus tachycardia, tachyarrhythmia, asymptomatic reduction of left ventricular ejection fraction, congestive heart failure, cardiomyopathies (see section 4.4 for associated signs and symptoms)
Uncommon	ECG abnormalities (e.g. nonspecific ST

	segment changes), myocardial infarction
Very rare	Pericarditis, myocarditis, atrioventricular and bundle branch block
Vascular disorders	
Common	Local phlebitis, thrombophlebitis, haemorrhages
Uncommon	Shock
Very rare	Thromboembolism, flush
Gastrointestinal disorders	
Very common	Nausea, vomiting, mucositis/stomatitis, diarrhoea, abdominal pain or burning sensation
Common	Gastrointestinal tract bleeding, bellyache
Uncommon	Oesophagitis, colitis (including severe enterocolitis / neutropenic enterocolitis with perforation)
Very rare	Gastric erosions or ulcerations
Hepatobiliary disorders	
Common	Elevation of the liver enzymes and bilirubin
Skin and subcutaneous tissue disorders	
Very common	Alopecia
Common	Rash, itch, hypersensitivity of irradiated skin (‘radiation recall reaction’)
Uncommon	Skin and nail hyperpigmentation, urticaria, cellulitis (this event can be severe), tissue necrosis
Very rare	Acral erythema
Not known	Local reaction
Renal and urinary disorders	
Very common	Red coloration of the urine for 1-2 days after the treatment
General disorders and administration site conditions	
Very common	Fever, headache, chills

Description of selected adverse reactions

Haematopoietic system

Pronounced myelosuppression is the most severe adverse effect of idarubicin treatment. However, this is necessary for the eradication of leukaemic cells (see section 4.4).

Cardiotoxicity

Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug (see section 4.4).

Gastrointestinal

Stomatitis and in severe cases ulceration of mucosa, dehydration caused by severe vomiting and diarrhoea; risk of perforation of colon etc.

Administration site

Phlebitis/thrombophlebitis and prevention measures discussed in section 4.2; unintended paravenous infiltrates may cause pain, severe cellulites and tissue necrosis.

Other adverse reactions: hyperuricaemia

Prevention of symptoms by hydration, urine alkalinisation, and prophylaxis with allopurinol may minimise potential complications of tumour lysis syndrome.

Paediatric population

Undesirable effects are similar in adults and children except a greater susceptibility to anthracycline-induced cardiac toxicity of children (see section 4.4).

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.

4.9 Overdose

Very high doses of idarubicin may be expected to cause acute myocardial toxicity within 24 hours and severe myelosuppression within one to two weeks. Delayed cardiac failure has been seen with the anthracyclines up to several months after the overdose. Patients treated with oral idarubicin should be observed for possible gastrointestinal haemorrhage and severe mucosal damage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anthracyclines and related substances

ATC Code: L01DB06

Idarubicin is a DNA intercalating anthracycline which interacts with the enzyme topoisomerase II and has an inhibitory effect on nucleic acid synthesis.

The modification of position 4 of the anthracycline structure gives the compound a high lipophilicity which results in an increased rate of cellular uptake compared with doxorubicin and daunorubicin.

Idarubicin has been shown to have a higher potency with respect to daunorubicin and to be an effective agent against murine leukaemia and lymphomas both by i.v. and oral routes. Studies *in-vitro* on human and murine anthracycline-resistant cells have shown a lower degree of crossresistance for idarubicin compared with doxorubicin and daunorubicin. Cardiotoxicity studies in animals have indicated that idarubicin has a better therapeutic index than daunorubicin and doxorubicin. The main metabolite, idarubicinol, has shown, *in-vitro* and *in-vivo,* antitumoural activity in experimental models. In the rat, idarubicinol administered at the same doses as the parent drug, is clearly less cardiotoxic than idarubicin.

In vitro studies have shown plasma protein binding of at least 95% for this product. This fact should be borne in mind when considering its use in combination with other drugs.

5.2 Pharmacokinetic properties

In adults, following oral administration of 10 to 60 mg/m^2 idarubicin, idarubicin was rapidly absorbed with the maximum plasma concentrations of 4-12.65 ng/mL achieved in 1 to 4 hours after dosing. The terminal half-life was 12.7±6.0 hrs (mean±SD). Following intravenous administration of idarubicin in adults, the terminal half-life was 13.9±5.9 hrs, similar to that observed after the oral administration.

After i.v. administration, idarubicin is extensively metabolised to an active metabolite, idarubicinol, which is slowly eliminated with a plasma $T_{½}$ ranging between 41-69 hours). The drug is eliminated by biliary and renal excretion, mostly in the form or idarubicinol.

Studies of cellular (nucleated blood and bone marrow cells) in leukaemic patients have shown that peak cellular idarubicin concentrations are reached a few minutes after injection.

Idarubicin and idarubicinol concentrations in nucleated blood and bone marrow cells are more than a hundred times the plasma concentrations. Idarubicin disappearance rates in plasma and cells were comparable, with a terminal half-life of about 15 hours. The terminal half-life of idarubicinol in cells was about 72 hours.

<u>Paediatric population</u>

Pharmacokinetic measurements in 7 paediatric patients receiving intravenous idarubicin hydrochloride in doses ranging from 15 to 40 mg/m^2 over the 3 days of treatment, showed a median idarubicin half-life of 8.5 hrs (range: 3.6-26.4 hrs). The active metabolite, idarubicinol, accumulated during the 3 days of treatment, exhibiting a median half-life of 43.7 hrs (range: 27.8-131 hrs). In a separate study, pharmacokinetic measurements in 15 paediatric patients receiving oral idarubicin hydrochloride in doses ranging from 30 to 50 mg/m^2 during the 3 days of treatment, the maximum plasma concentration of idarubicin was 10.6 ng/mL (range 2.7-16.7 ng/mL at the 40 mg/m^2 dose). The median terminal

half-life of idarubicin of was 9.2 hrs (range: 6.4-25.5 hrs). Significant accumulation of idarubicinol was seen over the 3 day treatment period. The observed terminal half-life value of idarubicin after i.v. was comparable to that following oral administration in paediatric patients.

Since C_{max} of idarubicin is similar in children and adults following oral administrations, absorption kinetics seem not to differ between adults and children.

Following both oral and i.v. administrations, the elimination half-life values of idarubicin in children and adults differ.

Total body clearance values of 30-107.9 L/h/m^2 for idarubicin reported for adults are higher than the values of 18-33 L/h/m^2 reported for paediatric populations. Although idarubicin has a very large volume of distribution in both adults and children, suggesting that much of the drug is bound to tissues, the shorter elimination half-life and lower total body clearance are not entirely explained by a smaller apparent volume of distribution in children compared to adults.

5.3 Preclinical safety data

Idarubicin has mutagenic properties and it is carcinogenic in rats.

Reproduction studies in animals have shown that idarubicin is embryotoxic and teratogenic in rats but not rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol

Water for injection

Hydrochloric acid, used for pH adjustment

6.2 Incompatibilities

Prolonged contact of Zavedos with any solution of an alkaline pH should be avoided as it will result in degradation of the drug.

Zavedos should not be mixed with heparin as a precipitate may form. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years

Opened vial

Each vial is for single use only and should be used immediately after opening. If not used immediately, in use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Unopened vial: Store and transport refrigerated (2°C - 8°C).

Opened vial: From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, this medicinal product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

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

6.5 Nature and contents of container

Glass vials which are closed with a siliconised, halobutyl rubber stopper and sealed with an aluminium cap with a plastic flip off top.
Zavedos is available in 5 mL, 10 mL and 20 mL vials packed singly in cartons. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Preparation and precautions:

The following protective recommendations are given due to the toxic nature of this substance:

- This product should be handled only by personnel who have been trained in the safe handling of such preparations.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling Zavedos should wear protective clothing: goggles, gowns and disposable gloves and masks.
- Any work surfaces used should be protected by disposable, plastic-backed, absorbent paper.
- The solution should not be allowed to contact mucous membranes, eyes or skin. Accidental contact with the skin and eyes should be treated immediately by copious lavage with water, or sodium bicarbonate solution, medical attention should be sought.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then with water.

Intravenous administration:

Zavedos must be administered only by the intravenous route. A slow administration over 5 to 10 minutes via the tubing of a freely running intravenous infusion of 0.9% sodium chloride, must be followed. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration, see section 4.4.

Disposal:

All items used for administration or cleaning, including gloves, should be placed in high risk, waste disposal bags for high temperature incineration.

For single use only. Any unused solution should be discarded.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited

Ramsgate Road

Sandwich

Kent CT13 9NJ, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00057/1520

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

04/02/2025