Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zavedos 5 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Idarubicin hydrochloride 5 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard Capsules
Opaque, red cap and body, self-locking, hard gelatin capsule, size No. 4, containing an orange powder. Imprinted 'IDARUBICIN 5'on the cap in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the treatment of acute myelogenous leukaemia (AML) intravenous chemotherapy is the first choice of remission induction.

Zavedos capsules are indicated for remission induction as part of attenuated combination regimes in elderly, previously untreated AML patients only when intravenous administration cannot be employed (e.g. for medical reasons, such as difficult venous access or psychological reasons such as refusal of i.v. treatment).

Zavedos capsules should not be used for palliative treatment of AML.

Zavedos capsules are intended for use under the direction of physicians experienced in leukaemia chemo-therapy.

4.2 Posology and method of administration

Dosage is usually calculated on the basis of body surface area.

In adult **AML** the recommended dose schedule is 30 mg/m^2 orally given daily for 3 days as a single agent, or between 15 and 30 mg/m^2 orally daily for 3 days in combination with other antileukemic agents.
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.
In patients with hepatic impairment a dose reduction of Zavedos should be considered (see section 4.4).
The capsules should be swallowed whole with some water and should not be sucked, bitten or chewed. Zavedos capsules may also be taken with a light meal.

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
- 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)

- uncontrolled infections

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. Therapy with Zavedos requires close observation of the patient and laboratory monitoring.

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.

Great caution should be exercised during the preparation and administration of Zavedos. Protective clothing and goggles should be worn by personnel. The solution should not be allowed to contact mucous membranes, eyes or skin of the patient.

Cardiac function
Myocardial toxicity as manifested by potentially fatal congestive heart failure, acute life-threatening arrhythmias or other cardiomyopathies may occur during therapy or several weeks after termination of therapy. Appropriate treatment should be considered. The risk of such myocardial toxicity may be higher following concomitant or previous radiation to the mediastinal-pericardial area or treatment with other potentially cardiotoxic agents or in patients with a particular clinical situation due to their disease (anaemia, bone marrow depression, infection, leukemic pericarditis and/or myocarditis). Other risk factors included active or dormant cardiovascular disease, previous therapy with anthracyclines and anthracenediones and the concomitant use of drugs with the ability to suppress cardiac contractility.

Cardiac function should be carefully monitored during treatment in order to minimise the risk of cardiac toxicity of the type described for other anthracycline compounds.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.

On the basis of the recommended dosage schedules the total cumulative dose administered over two courses can be expected to reach 60 - 80 mg/m^2.

Cumulative dose limits for i.v or oral idarubicin hydrochloride have not been defined, a specific cardiological evaluation in cancer patients showed no significant modifications of cardiac function in patients treated with Zavedos at a mean cumulative dose of 93 mg/m^2. 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/m2 suggest a low probability of cardiotoxicity.

Early clinical diagnosis of drug-induced myocardial damage appears to be important for pharmacological treatment to be useful.
As with other anthracylcines, care must be taken when administering Zavedos to children because of the increased risk of cardiotoxicity from these products in the age group.

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.

Haematologic toxicity
Idarubicin is a potent bone marrow suppressant. Myelosuppression, primarily of leukocytes, will therefore occur in all patients given a therapeutic dose of this agent and careful haematological monitoring including granulocytes, red cells and platelets is required.

The drug should not be given to patients with pre existing bone-marrow suppression induced by previous drug therapy or radiotherapy unless the benefit warrants the risk.

Severe myelosuppression will occur in all patients given a therapeutic dose of this agent.

Haematologic 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 this 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.

Facilities with laboratory and supportive resources adequate to monitor drug tolerability and protect and maintain a patient compromised by drug toxicity should be available. It must be possible to treat rapidly and completely a severe haemorrhagic condition and/or severe infection.

Patients aged over 55 years should be given vigorous supportive treatment during the aplastic period.

Secondary leukaemia

Secondary leukaemia, with or without a preleukemic 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 pretreated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukaemias can have a 1- to 3-year latency period.

Gastrointestinal

Idarubicin is emetigenic. 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.

Carcinogenesis

Zavedos has mutagenic properties and it is carcinogenic in rats. Its carcinogenic potential in man is unknown. The possibility of a carcinogenic effect should be kept in mind in planning long-term therapy.

Hepatic and/or 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 to 2.0-mg %.

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 and restarted in another vein.
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 alkalinization, and prophylaxis with allopurinol to prevent hyperuricaemia may minimize potential complications of tumour lysis syndrome. Appropriate measures must be taken to control any systemic infection before beginning therapy.

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

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 interactions

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

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).
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 coadminstration 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

Food does not appear to reduce idarubicin absorption and Zavedos may therefore be given with a light meal.

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. For this reason, males undergoing treatment with idarubicin should use effective contraceptive methods for at least 3.5 months after the last dose (see section 4.4). Both men and women should seek advice on fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

Special care should be taken if it is essential that patients drive or operate machinery while undergoing treatment especially if in a debilitated condition.

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 leukemic 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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Although the single-dose packaging is designed to minimise the risk of overdosage and no data on overdosage exists, should this occur, gastric lavage should be carried out as soon as possible. Patients treated with oral idarubicin should be observed for possible gastrointestinal haemorrhage and severe mucosal damage. Very high doses of idarubicin may be expected to cause acute myocardial toxicity within 24 hours and severe myelosuppression within one or two weeks. Treatment should further aim to support the patient during this period and should utilise such measures as blood transfusions and reverse barrier nursing. Delayed cardiac failure has been seen with the anthracyclines up to several months after the overdose. Patients should be observed carefully and if signs of cardiac failure arise, should be treated along conventional lines.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: L01DB06, Pharmacotherapeutic group: Anthracyclines and related substances

Idarubicin is an antimitotic and cytotoxic agent which intercalates with DNA an inhibitory effect on nucleic acid synthesis.
The compound has 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 iv and oral routes. Studies in vitro on human and murine anthracycline-resistant cells have shown a lower degree of cross-resistance 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, antitumoral activity in experimental models. In the rat, idarubicinol, administered at the same dose as the parent drug, is clearly less cardiotoxic than idarubicin.

5.2 Pharmacokinetic properties

After oral administration to patients with normal renal and hepatic function, idarubicin is rapidly absorbed, with a peak time of 2-4 hours, is eliminated from systemic circulation with a terminal plasma $t_{½}$ ranging between 10-35 hours and is extensively metabolized to an active metabolite, idarubicinol, which is more slowly eliminated with a plasma $t_{½}$ ranging between 33 and 60 hours. The drug is mostly eliminated by biliary excretion, mainly in the form of idarubicinol, urinary excretion accounting for 1-2% of the dose as unchanged drug and for up to 4.6% as idarubicinol.
Average values of absolute bioavailability have been shown to range between 18 and 39%, whereas the average values calculated on the data from the active metabolite, idarubicinol, are somewhat higher (29-58%). The effective bioavailability, calculated on the basis of the pharmacological response, is approximately 35%.
Studies on cellular (nucleated blood and bone marrow cells) drug concentrations in leukemic patients have shown that uptake is rapid and almost parallels the appearance of the drug in plasma. Idarubicin and idarubicinol concentrations in nucleated blood and bone marrow cells are more than two hundred times the plasma concentrations. Idarubicin and idarubicinol disappearance rates in plasma and cells were almost comparable.

5.3 Preclinical safety data

Idarubicin given orally is about three times less toxic than when given by the i.v. route; in particular, there is no increase of the gastro-intestinal toxicity when the compound is given orally.

The target organs of oral idarubicin were qualitatively similar to those observed with intravenous idarubicin and other anthracycline compounds and included: the haemolymphopoietic and immune systems, gastro-intestinal tract, heart, liver, kidneys and testes. The liver and kidneys were generally more affected by the intravenous route than by the oral route, while the gastro-intestinal tract and testes were similarly affected.
Idarubicin, like other anthracyclines, must be considered mutagenic, teratogenic and potentially carcinogenic, even if administered orally.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Glyceryl Palmito-Stearate

Capsule Shell:
Red iron oxide (E172)
Titanium Dioxide (E171)
Gelatin

Printing Ink:
Shellac

Black iron oxide (E172)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

The capsules are contained in amber glass bottles (type III). One capsule per bottle in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

Personnel handling idarubicin should wear protective clothing: goggles, gowns and disposal gloves and masks. The capsules should be handled by personnel who have been trained in the safe handling of cytotoxic preparations and whom have consulted local cytotoxic guidelines.

Pregnant personnel should be excluded from working with this drug.

Before administration it should be ensured that the capsules are intact. They should be swallowed whole with some water and should not be sucked, bitten or chewed.
In case of accidental contact of the powder from the capsule with the eye, skin or mucosa, the area should be immediately and thoroughly rinsed with water; medical attention should be sought.

All materials that have been utilised for administration should be disposed of according to local standard hospital procedures.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/142/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 30 May 2008

10 DATE OF REVISION OF THE TEXT

January 2022