Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vinblastine Sulfate 1mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 1.0 mg vinblastine sulfate

Each 10 ml vial contains 10 mg of vinblastine sulfate

Excipient(s) with known effect:
Vinblastine Sulfate 1 mg/ml solution for injection or infusion contains 35.42 mg sodium in each 10 ml vial.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

A clear, colourless, sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vinblastine Sulfate is used either alone or in combination with other neoplastic agents, in the treatment of Hodgkin's Disease (Stages III and IV); lymphocytic lymphoma (nodular and diffuse, poorly and well differentiated); histiocytic lymphoma; advanced stages of mycosis fungoides; advanced carcinoma of the testis; Kaposi's sarcoma and Letterer-Siwe disease (histocytosis X). Vinblastine Sulfate may be used in the treatment of choriocarcinoma resistant to other chemotherapeutic agents; carcinoma of the breast, unresponsive to appropriate endocrine surgery and hormonal therapy.

4.2 Posology and method of administration

FOR INTRAVENOUS USE ONLY.
FATAL IF GIVEN BY OTHER ROUTES(see section 4.4)

In case of mistaken administration by the intrathecal route, see section 4.4.

Posology

Vinblastine Sulfate is given intravenously at weekly intervals according to the needs of the patient. Therapy is initiated by a single intravenous dose in accordance with the following dosage table, and white blood cell counts should be made to determine the sensitivity of the patient to vinblastine. Dosage should not be increased after that dose which reduces the white cell count to approximately 3000 cells/mm^3.

	Adults mg/m^2 bsa	Children mg/m^2 bsa
First Dose	3.7	2.5
Second Dose	5.5	3.75
Third Dose	7.4	5.0
Fourth Dose	9.25	6.25
Fifth Dose	11.1	7.5

Dosage increase may be continued but must not exceed 18.5 mg/m^2 for adults or 12.5 mg/m^2 for children.

Patients should be maintained on the maximum weekly dose that does not cause the above degree of leucopenia (3,000 cells/mm^3).

For most adult patients this dosage will be 5.5 mg/m^2 - 7.4 mg/m^2, however, leucopenia can be produced at 3.7 mg/m^2, other patients may require 11.1 mg/m^2 and, very rarely, 18.5 mg/m^2. For testicular tumours, the dosage may be increased to 0.2 mg/kg administered on each of two consecutive days every three weeks.

A FURTHER DOSE OF VINBLASTINE SHOULD NOT BE GIVEN UNTIL THE WHITE CELL COUNT HAS RETURNED TO AT LEAST 4000/mm3, EVEN THOUGH 7 DAYS MAY HAVE ELAPSED.

In some cases, oncolytic activity may be encountered before the leucopenic effect and, when this occurs, there is no necessity to increase subsequent doses.

To minimise the possibility of extravascular spillage, it is suggested that the syringe and needle be rinsed with venous blood before withdrawal. The dose should not be diluted in large volumes of diluent (i.e., 100 to 250 ml) or given intravenously for prolonged periods (ranging from 30 to 60 minutes or more), since this frequently results in irritation of the vein and increases the chance of extravasation.
Because of the enhanced possibility of thrombosis, it is considered inadvisable to inject a solution of vinblastine sulfate into an extremity in which the circulation is impaired, or potentially impaired, by such conditions as compressing or invading neoplasm, phlebitis or varicosity.

Patients with hepatic impairment
As vinblastine sulfate is metabolised and excreted principally by the liver, toxicity may be increased when there is hepatic insufficiency and it may be necessary to reduce initial doses in the presence of significantly impaired hepatic or biliary function. A reduction of 50% in the dose is recommended for patients having a direct serum bilirubin value above 3 mg/100 ml.

Patient with renal impairment
Since metabolism and excretion are primarily hepatic, no modification is recommended for patients with impaired renal function.

Duration of treatment
Duration of maintenance therapy is dependent upon the disease state and the antineoplastic agent combination and the condition of the patient.

Differing clinical opinions are held for the appropriate duration of maintenance therapy in Hodgkin's Disease. Prolonged chemotherapy for maintaining remissions involves several risks such as life-threatening infections, sterility and possibly the appearance of other cancers through suppression of immune response.

Method of administration
Vinblastine should not be given intramuscularly, subcutaneously or intrathecally.

It is recommended to infuse Vinblastine Sulfate over 5 to 10 minutes after dilution in Sodium Chloride 0.9% to a final volume of 50 ml to 100 ml with a final concentration between 0.04 and 0.4mg/ml.

Alternatively, Vinblastine Sulfate may be injected directly into a vein over about one minute.

Syringes containing this product should be over labelled with the warning label provided: **'FOR INTRAVENOUS USE ONLY. FATAL IF GIVEN BY OTHER ROUTES'.**

4.3 Contraindications

FOR INTRAVENOUS USE ONLY.
FATAL IF GIVEN BY OTHER ROUTES (see section 4.4)

Vinblastine Sulfate is contraindicated in patients who are leucopenic unless result of disease being treated. It should not be used in the presence of untreated infection. Such infections should be brought under control with antiseptics or antibiotics before the initiation of therapy with Vinblastine Sulfate.

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

4.4 Special warnings and precautions for use

Vinblastine Sulfate is for intravenous use only (see section 4.2).
It should only be administered under the direction of a specialist oncology service having the facilities for regular monitoring of clinical biochemical and haematological effects during and after administration. Cytotoxic preparations should not be handled by pregnant staff.

Syringes containing this product should be over labelled with the warning label provided: **'FOR INTRAVENOUS USE ONLY. FATAL IF GIVEN BY OTHER ROUTES'.**

After inadvertent intrathecal administration of vinca alkaloids, immediate neurosurgical intervention is required in order to prevent ascending paralysis leading to death. In a very small number of patients, life-threatening paralysis and subsequent death was averted but resulted in devastating neurological sequelae, with limited recovery afterwards.
Based on the published management of survival cases involving the related vinca alkaloid vincristine sulfate, if Vinblastine Sulfate is mistakenly given by the intrathecal route, the following treatment should be initiated immediately after the administration:

1. Removal of as much cerebrospinal fluid (CSF) as is safely possible through the lumbar access.
2. Insertion of an epidural catheter into the subarachnoid space via the intervertebral space above initial lumbar access and CSF irrigation with lactated Ringer's solution. Fresh frozen plasma should be requested and, when available, 25ml should be added to every 1 litre of lactated Ringer's solution.
3. Insertion of an intraventricular drain or catheter by a neurosurgeon and continuation of CSF irrigation with fluid removal through the lumbar access connected to a closed drainage system. Lactated Ringer's solution should be given by continuous infusion at 150ml/hour, or at a rate of 75ml/hour when fresh frozen plasma has been added as above.

The rate of infusion should be adjusted to maintain a spinal fluid protein level of 150mg/dl.

The following measures have also been used in addition but may not be essential:

Glutamic acid has been given IV 10gm over 24 hours, followed by 500mg tds by mouth for 1 month. Folinic acid has been administered intravenously as a 100mg bolus and then infused at a rate of 25mg/h for 24 hours, then bolus doses of 25mg 6-hourly for 1 week. Pyridoxine has been given at a dose of 50mg 8-hourly by intravenous infusion over 30 minutes. Their roles in the reduction of neurotoxicity are unclear.

As with other antineoplastic agents, vinblastine may cause a severe local reaction on extravasation. If leakage into the surrounding tissue should occur during intravenous administration of Vinblastine Sulfate, it should be discontinued immediately and any remaining portion of the dose should be introduced into another vein. Local injection of hyaluronidase with the application of heat has been used to disperse the drug in order to minimise discomfort and the possibility of tissue damage. Cases of phlebitis and cellulitis have been reported.
Aspermia has been reported in men. Sperm abnormalities have been noticed in mice. Additional studies in mice demonstrated no reduction in fertility in males. Amenorrhoea has occurred in some patients treated with Vinblastine Sulfate in combination with other drugs. Recovery of menses was frequent.

There is no currently available evidence to indicate that Vinblastine Sulfate itself has been carcinogenic in humans, although some patients have developed leukaemia following radiation therapy and the administration of Vinblastine Sulfate in combination with alkylating agents.

Stomatitis and neurological toxicity, although not common or permanent, can be disabling. Liver disease may alter the elimination of vinblastine in the bile, markedly increasing toxicity to peripheral nerves and necessitating a dosage modification in affected patients. Toxicity is increased in patients with obstructive jaundice.

The dose-limiting factor is myelosuppression. In general, the larger the dose employed the more profound and longer lasting the leucopenia will be. The fact that the granulocyte count returns to normal levels after drug-induced leucopenia is an indication that the granulocyte-producing mechanism is not permanently depressed.
Following therapy with Vinblastine Sulfate, the nadir in the granulocyte count may be expected to occur five to ten days after the last day of drug administration. Recovery of the granulocyte count is fairly rapid thereafter and is usually complete within another seven to fourteen days. If granulocytopenia with less than 1,000 granulocytes/mm^3 occurs following a dose of

Vinblastine Sulfate, the patient should be watched carefully for evidence of infection until the granulocyte count has returned to a safe level. Any infection must be brought under control immediately.

Patients should be carefully monitored for infection until the white cell count has returned to normal levels, if leucopenia with less than 2000 white blood cells per mm^3 occurs following a dose of Vinblastine Sulfate.

When cachexia or ulcerated areas of the skin are present, a more profound granulocytopenic response may be produced by vinblastine. Therefore, its use should be avoided in older persons suffering from either of these conditions.

Although the thrombocyte count is not usually significantly lowered by therapy with Vinblastine Sulfate, patients whose bone marrow has been recently impaired by prior therapy with radiation or with other oncolytic drugs may show thrombocytopenia (less than 150,000 platelets/mm^3). When other chemotherapy or radiation has not been employed previously, thrombocyte reduction below the level of 150,000/mm^3 is rarely encountered, even when Vinblastine Sulfate may be causing significant granulocytopenia. Rapid recovery from thrombocytopenia within a few days is the rule.

The effect of Vinblastine Sulfate upon the red blood cell count and hemoglobin is usually insignificant when other treatment does not complicate the picture.
Granulocyte and platelet counts have sometimes fallen precipitously after moderate doses of Vinblastine Sulfate in patients with malignant cell infiltration of the bone marrow. Further use of the drug in such patients is inadvisable.

Breaks and aberrations were not observed on chromosome analysis of marrow cells from patients treated with Vinblastine Sulfate although chromosomal changes have been noted in some hamster lung cell *in vitro* tests.

The use of small amounts of Vinblastine Sulfate daily for long periods is not advisable, even though the resulting total dosage may be similar to the recommended dosage. Little or no therapeutic advantage has been demonstrated when such regimens have been used and side-effects are increased.

Avoid contamination of the eye with Vinblastine Sulfate solution. If accidental contamination occurs, severe irritation or corneal ulceration may result. The affected eye should be thoroughly irrigated with water immediately.

Excipient information
Vinblastine Sulfate contains 35.42 mg sodium in each vial, equivalent to 1.77% of the WHO maximum recommended daily intake (RDI) of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Vinblastine Sulfate used as part of a combination regimen with mitomycin may result in fatal acute respiratory distress or failure and pulmonary infiltration or pulmonary oedema.

Cases of respiratory distress with interstitial pulmonary infiltrates have been reported in patients given a regimen comprising vinblastine, mitomycin, with or without progesterone (MVP or MV). Dyspnoea and severe bronchospasm have been reported following the administration of the vinca alkaloids. These reactions have been encountered most frequently when the vinca alkaloid was used in combination with mitomycin-C and may be serious when there is pre-existing pulmonary dysfunction. The onset may be within minutes, or several hours after the vinca is injected, and may occur up to 2 weeks following a dose of mitomycin. Progressive dyspnoea, requiring chronic therapy, may occur. Vinblastine Sulfate should not be readministered.
Co-administration of cisplatin has been reported to cause higher plasma concentrations of vinblastine sulfate and severity of neutropenia may be altered when given in conjunction with cisplatin.

Following combined treatment with vinblastine, bleomycin and cisplatin, there have been reports of a decline in glomerular filtration rate which may be reversible, nephrotoxicity, pulmonary toxicity, peripheral sensory neuropathy, neurotoxicity, ototoxicity, azoospermia, irreversible high frequency hearing loss, Raynaud's phenomenon with digital ischemia and gangrene and other vascular events (such as myocardial infarction and cerebrovascular accident).

Earlier onset and increased severity of side effects have been reported during concurrent administration of vinca alkaloids with inhibitors of the hepatic isoenzyme cytochrome P450 subfamily CYP3A.
Erythromycin may increase the toxicity of vinblastine sulfate which may cause increased severity of neutropenia, myalgia and constipation.

Serum levels of anticonvulsants may be reduced by cytotoxic drug regimes, which include vinblastine.

The simultaneous oral or intravenous administration of phenytoin and anti- neoplastic chemotherapy combinations that included vinblastine sulfate have been reported to reduce blood levels of the anticonvulsant and to increase seizure activity. Although the contribution of the vinca alkaloids has not been established, dosage adjustment of phenytoin, based on serial blood level monitoring, may need to be made when it is used in combination with vinblastine.

Particular caution is warranted when Vinblastine Sulfate is used in combination with other agents known to be ototoxic, such as the platinum-containing oncolytics.

When chemotherapy is being given in conjunction with radiation therapy through portals which include the liver, the use of Vinblastine Sulfate should be delayed until radiation therapy has been completed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Although information on the use of vinblastine during pregnancy is limited, the drug may cause foetal toxicity when administered to pregnant women. The drug causes resorption of foetuses in animals and produces gross foetal abnormalities in surviving offspring. There are no adequate and controlled studies to date using vinblastine in pregnant women, and the drug should be used during pregnancy only in life-threatening situations or severe disease for which safer drugs cannot be used or are ineffective. Women of childbearing potential should be advised to avoid becoming pregnant while receiving the drug. When vinblastine is administered during pregnancy or the patient becomes pregnant while receiving the drug, the patient should be informed of the potential hazard to the foetus.

Breast-feeding

It is not known whether vinblastine is excreted in human milk. Because of the potential for serious adverse reactions due to vinblastine in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Fertility

The effect of vinblastine on fertility in humans is not fully known. Aspermia has occurred in some individuals during vinblastine therapy.

4.7 Effects on ability to drive and use machines

Vinblastine Sulfate has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The frequency grouping is defined using the following convention: Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations	
Not known	Pharyngitis
Neoplasms benign, malignant and unspecified (incl. cysts and polys)	
Not known	Tumour pain
Blood and lymphatic system disorders	
Not known	Neutropenia, Leucopenia[a], Thrombocytopenia, Anaemia
Endocrine disorders	
Not known	Inappropriate anti-diuretic hormone secretion[b]

Metabolism and nutrition disorders	
Not known	Anorexia
Psychiatric disorders:	
Not known	Depression
Nervous system disorders	
Not known	Cerebrovascular accident[c], Convulsions, Neurotoxicity[d], Numbness, Neuropathy peripheral, Loss of deep tendon reflexes, Paraesthesia, Headache, Dizziness
Ear and labyrinth disorders	
Not known	VIIIth nerve injury[e]
Cardiac disorders	
Not known	Myocardial infarction[c]
Vascular disorders	
Not known	Hypertension[c], Raynaud's phenomenon[c]
Respiratory, thoracic and mediastinal disorders	
Not known	Dyspnoea, Severe bronchospasm
Gastrointestinal disorders	
Not known	Haemorrhagic enterocolitis, Rectal bleeding, Peptic ulcer haemorrhage, Ileus, Nausea[f], Vomiting[f], Constipation[g], Oral mucosal blistering, Diarrhoea, Abdominal pain, Stomatitis
Skin and subcutaneous tissue disorders	
Not known	Vesiculation of the skin, Alopecia[h], Ulceration of the skin
Musculoskeletal and connective tissue disorders	
Not known	Myalgia, Bone pain, Jaw pain
Reproductive system and breast disorders	
Not known	Aspermia
General disorders and administration site conditions	
Not known	Injection site phlebitis, Injection site cellulitis (and in extreme cases skin exfoliation), Extravasation, Malaise, Weakness

[a] Leucopenia is the most common side effect and dose limiting factor. The nadir of the white cell count generally occurs 5 to 10 days after the last dose of initial treatment.

[b] Reported with higher than recommended doses. Cases of inappropriate secretion of antidiuretic hormone have been observed in patients treated with vinca alkaloids including vinblastine.

[c] In combination chemotherapy with Vinblastine Sulfate, bleomycin and cisplatin.

[d] The incidence of neurotoxicity is dose dependent.

[e] Manifestations include partial or total deafness, which may be temporary or permanent, and difficulties with balance, including dizziness, nystagmus and vertigo.

[f] Antiemetics may be used to control nausea and vomiting.

[g] May take the form of upper colon impaction.

[h] Alopecia is usually not total and in some cases the hair regrows during maintenance therapy.

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

Side effects following the use of vinblastine are dose related. Therefore, following administration of more than the recommended dose, patients can be expected to experience these effects in an exaggerated fashion. Any dose that results in elimination of platelets and neutrophils from blood and marrow and their precursors from marrow is life-threatening.

The major effect of excessive doses of vinblastine will be on granulocytopoeisis, and this may be life-threatening.

Overdoses occurring during prolonged, consecutive day infusions may be more toxic than the same total dose given by rapid intravenous administration.

In addition, neurotoxicity similar to that seen with vincristine sulphate may be observed.

Treatment: Supportive care should include:

(1) prevention of the side effects that result from the syndrome of inappropriate secretion of antidiuretic hormone. This includes restriction of fluid intake and perhaps the use of a diuretic acting on the loop of Henle and distal tubule function;
(2) administration of an anticonvulsant;
(3) prevention and treatment of ileus;
(4) monitoring the patient's cardiovascular system; and
(5) daily blood counts for guidance in transfusion requirement and assessing therisk of infection.

There is no specific antidote. The use of folinic acid in addition to the other supportive measures recommended may be considered, although, unlike vincristine sulfate, studies have not been conducted to confirm its protective action.

There is no information regarding the effectiveness of dialysis nor of cholestyramine for the treatment of overdose.

Vinblastine Sulfate in the dry state is irregularly and unpredictably absorbed from the gastro- intestinal tract following oral administration. Absorption of the solution has not been studied. If Vinblastine Sulfate is swallowed, activated charcoal in a water slurry may be given by mouth along with a cathartic. The use of cholestyramine in this situation has not been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vinca alkaloids and analogues, ATC code: L01CA01

Vinblastine Sulfate is a cytotoxic drug that arrests cell growth at the metaphase. Its actions are more pronounced on the rapidly dividing cell than on the normal cell. It appears to act, like Vincristine, by binding to the microtubular proteins of the mitotic spindle, preventing polymerisation.

Although the mechanism of action has not been definitely established, vinblastine appears to bind to or crystallise critical microtubular proteins of the mitotic spindle, thus preventing their proper polymerisation and causing metaphase arrest. In high concentrations, vinblastine also exerts complex effects on nucleic acid and protein synthesis. Vinblastine reportedly also interferes with amino acid metabolism by blocking cellular utilisation of glutamic acid and thus inhibits purine synthesis, the citric acid cycle, and the formation of urea. Vinblastine exerts some immunosuppressive activity.

5.2 Pharmacokinetic properties

Vinblastine Sulfate is unpredictably absorbed from the GI tract. Following intravenous administration, the drug is rapidly cleared from the blood and distributed into body tissues.

Vinblastine crosses the blood-brain barrier poorly and does not appear in the CSF in therapeutic concentrations. Vinblastine is reported to be extensively metabolised, primarily in the liver, to desacetylvinblastine, which is more active than the parent compound on a weight basis. The drug is excreted slowly in urine and in faeces via the bile.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Sodium hydroxide Sulphuric acid

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Vinblastine Sulfate is incompatible with furosemide, when injected sequentially into Y-site with no flush between or when mixed in syringe. Immediate precipitation results.

6.3 Shelf life

2 years.

After dilution chemical and physical in-use stability has been demonstrated for:

Diluent	Target Concentration	Storage Conditions	Time period
0.9% (9 mg/ml) sodium chloride solution for infusion	0.04 mg/ml	2-8^{o}C in the absence of light in non-PVC (polyolefin) infusion bags	19 days
0.9% (9 mg/ml) sodium chloride solution for infusion	0.4 mg/ml	2-8^{o}C in the absence of light in non-PVC (polyolefin) infusion bags	35 days

From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 - 8°C). Keep the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

10 ml, 20 mm Type I clear glass vial, rubber closure, aluminium seal with plastic flip-off top, in packs of 5 vials. Each vial is wrapped in a clear, plastic (ONCO-TAINÒ) protective sleeve.

6.6 Special precautions for disposal and other handling

Cytotoxic Handling Guidelines

Administration

Should be administered only by or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

For instructions on administration, see section 4.2.

Preparation(Guidelines)

Refer to local cytotoxic guidelines before commencing.

a) Chemotherapeutic agents should be prepared for administration only by professionals who have been trained in the safe use of the preparation.

b) Operations such as reconstitution of powder and transfer to syringes should be carried out only in the designated area.

c) The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.

d) Pregnant personnel are advised not to handle chemotherapeutic agents.

e) Refer to local cytotoxic guidelines before commencing.

For dilution of the medicinal product before administration:
Determine the dose of Vinblastine Sulfate to be administered (based upon the recommended dose and the patient's body surface area). Draw the appropriate volume of Vinblastine Sulfate up into a sterile syringe. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in Vinblastine Sulfate.

The appropriate dose of Vinblastine Sulfate must be diluted in Sodium Chloride 0.9% to a final volume of 50 ml to 100 ml with a final concentration between 0.04 and 0.4mg/ml.

Contamination

a) In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat the transient stinging of skin. Medical advice should be sought if the eyes are affected.

b) In the event of spillage, operators should put on gloves and mop up the spilled material with a sponge kept in the area for that purpose. Rinse the area twice with water. Put all solutions and sponges into a plastic bag and seal it.

Disposal

Use immediately, discard any unused portions.
Syringes, containers, absorbent materials, solution and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA0822/208/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

October 2023