SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tamoxifen 40mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:Tamoxifen Citrate 60.80mg

Excipient with known effect:
Each tablet contains 519.20mg of lactose.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets
White, convex tablets with an approximate diameter of 12.5mm, printed T40on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tamoxifen tablets are indicated for:

1. The treatment of breast cancer.

2. The treatment of anovulatory infertility.

4.2 Posology and method of administration

Posology
Breast Cancer

Adults:The recommended daily dose of tamoxifen is normally 20mg. No additional benefit in terms of delayed recurrence or improved survival in patients has been demonstrated with higher doses. Substantive evidence supporting the use of treatment with 30-40mg per day is not available, although these doses have been used in some patients with advanced disease.

Elderly: The same dosage regimens of tamoxifen have been used in elderly patients with breast cancer and in some of these patients it has been used as sole therapy.

Anovulatory Infertility

The possibility of pregnancy must be excluded before commencing any course of treatment whether initial or subsequent.

The initial course of treatment in women menstruating regularly but with anovular cycles, consists of 20mg of tamoxifen daily in the second, third, fourth and fifth days of the menstrual cycle.

Should the initial course of treatment, as judged by unsatisfactory basal temperature records and poor pre-ovulatory cervical mucus, prove unsuccessful, further courses of treatment may be given during subsequent menstrual periods, increasing the dosage to 40mg and then 80mg daily.

In women with irregular menstrual cycle, the initial course of treatment may begin on any day. Should there be no sign of ovulation, then a subsequent course of treatment may begin 45 days later with dosage increased to 40mg and then 80mg daily. If a patient responds with menstruation then the next course of treatment is commenced on the second day of the cycle.

Use in children
The use of Tamoxifen is not recommended in children, as safety and efficacy have not been established (see sections 5.1 and 5.2).

Method of administration
Tamoxifen tablets are for oral administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Tamoxifen must not be given during pregnancy. Pre-menopausal patients must be carefully examined before treatment for breast cancer or infertility to exclude the possibility of pregnancy. (See also Section 4.6)

Concurrent anastrozole therapy (see section 4.5).

Treatment for infertility: Patients with a personal or family history of confirmed idiopathic venous thromboembolic events or a known genetic defect.

4.4 Special warnings and precautions for use

Menstruation is suppressed in a proportion of pre-menopausal women receiving Tamoxifen for the treatment of breast cancer.

An increased incidence of endometrial changes including hyperplasia, polyps, cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours), has been reported in association with Tamoxifen treatment. The underlying mechanism is unknown, but may be related to the oestrogen-like effect of Tamoxifen. Any patient receiving or having previously received Tamoxifen who report abnormal gynaecological symptoms, especially vaginal bleeding, or who presents with menstrual irregularities, vaginal discharge and symptoms such as pelvic pain or pressure should be promptly investigated.

Studies in premenopausal women who were treated with tamoxifen for reduction of breast cancer risk or in the management of breast cancer have reported decreases in bone mineral density. Premenopausal women taking Tamoxifen should be advised regarding measures to maintain bone health, according to local clinical guidelines.

A number of second primary tumours, occurring at sites other than the endometrium and the opposite breast, have been reported in clinical trials, following the treatment of breast cancer patients with Tamoxifen. No causal link has been established and the clinical significance of these observations remains unclear.

Venous thromboembolism:

- A 2-3-fold increase in the risk for VTE has been demonstrated in healthy tamoxifen-treated women (see section 4.8).
- In patients with *breast cancer*, prescribers should obtain careful histories with respect to the patient's personal and family history of VTE. If suggestive of a prothrombic risk, patients should be screened for thrombophillic factors. Patients who test positive should be counselled regarding their thromobotic risk. The decision to use tamoxifen in these patients should be based on the overall risk to the patient. In selected patients, the use of tamoxifen with prophylactic

anticoagulation may be justified (cross-reference section 4.5)

- The risk of VTE is further increased by severe obesity, increasing age and all other factors for VTE. The risks and benefits should be carefully considered for *all* patients before treatment with tamoxifen. In patients with *breast cancer*, this risk is also increased by concomitant chemotherapy (see section 4.5). Long-term anti-coagulant prophylaxis may be justified for some patients with *breast cancer* who have multiple risk factors for VTE.
- Surgery and immobility: For patients being treated for *infertility*, tamoxifen should be stopped at least 6 weeks before surgery or long-term immobility (when possible) and restarted only when the patient is fully mobile. For patients with *breast cancer* tamoxifen treatment should only be stopped if the risk of tamoxifen-induced thrombosis clearly outweighs the risks associated with interrupting treatment. All patients should receive appropriate thrombosis prophylactic measures and should include graduated compression stockings for the period of hospitalisation, early ambulation, if possible, and anti-coagulant treatment.
- If *any* patient presents with VTE, tamoxifen should be stopped immediately and appropriate anti-thrombosis measures initiated. In patients being treated for *infertility*, tamoxifen should not be re-started unless there is a compelling alternative explanation for their thrombotic event. In patients receiving tamoxifen for *breast cancer* the decision to re-start tamoxifen should be made with respect to the overall risk for the patient. In selected patients with *breast cancer*, the continued use of tamoxifen with prophylactic anticoagulation may be justified.
- *All* patients should be advised to contact their doctors immediately if they become aware of any symptoms of VTE.
- In delayed microsurgical breast reconstruction tamoxifen may increase the risk of microvascular flap complications.
- In an uncontrolled trial in 28 girls aged 2–10 years with McCune Albright Syndrome (MAS), who received 20 mg once a day for up to 12 months duration, mean uterine volume increased after 6 months of treatment and doubled at the end of the one-year study. While this finding is in line with the pharmacodynamic properties

of tamoxifen, a causal relationship has not been established.

Tamoxifen at the recommended dose, may prolong the QTc interval on the electrocardiogram (ECG).

ECG and electrolyte monitoring are recommended in patients with underlying risks of QT prolongation and cardiac comorbidities such as:
• Long QT syndrome
• Clinically significant or uncontrolled heart disease, such as congestive heart failure, recent myocardial infarction, and cardiac conduction and repolarisation abnormalities
• Concomitant use of QT prolonging medicines
• Electrolyte abnormalities

ECG should be assessed before initiating treatment and follow-up ECG should be repeated once tamoxifen has reached steady state concentrations (at least 4 weeks). ECG monitoring thereafter should be done as clinically indicated for patient specific risk factors, i.e. introduction or dose changes of QT prolonging medicines, electrolyte abnormalities, new symptoms (e.g. palpitations, dizziness, syncope).

Appropriate monitoring of serum electrolytes (including potassium, magnesium, calcium, phosphate) should be performed before initiating treatment and during treatment as clinically indicated. Any abnormalities should be corrected prior to initiating tamoxifen and during treatment.

In the literature it has been shown that CYP2D6 poor metabolisers have a lowered plasma level of endoxifen, one of the most important active metabolites of tamoxifen (see section 5.2).

Concomitant medications that inhibit (CYPD2D6 may lead to reduced concentrations of the active metabolite endoxifen. Therefore, potent inhibitors of CYP2D6 (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided during tamoxifen treatment (see section 4.5 and 5.2).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine because it contains lactose
Pharmacokinetic interaction with CYP2D6 inhibitors, showing a reduction in plasma level of an active tamoxifen metabolite, 4-hydroxy-Ndesmethyltamoxifen (endoxifen), has been reported in the literature. The relevance of this to clinical practice is not known.

Pharmacokinetic interaction with CYP2D6 inhibitors, showing a 65-75% reduction in plasma levels of one of the more active forms of the drug, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants (e.g. paroxetine) in some studies. As a reduced effect of tamoxifen cannot be excluded, co-

administration with potent CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided (see section 4.4 and 5.2).

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be lifethreatening or fatal, have been reported in association with tamoxifen treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, tamoxifen should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed a serious reaction such as SJS or TEN with the use of tamoxifen, treatment with tamoxifen must not be restarted in this patient at any time.

In patients with hereditary angioedema, tamoxifen may induce or exacerbate symptoms of angioedema.

4.5 Interaction with other medicinal products and other forms of interac

Tamoxifen at the recommended dose may prolong the QTc interval on the electrocardiogram (ECG), and the concomitant use of Tamoxifen with other medicinal products known to prolong the QT interval may further potentiate QT prolongation. Therefore, caution is advised in case of such combination, and ECG and electrolyte monitoring are recommended in such patients (see section 4.4).

When tamoxifen is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. When such coadministration is initiated, careful monitoring of the patient is recommended.

When tamoxifen is used in combination with cytotoxic agents for the treatment of breast cancer, there is an increased risk of thromboembolic events occurring. (See also Section 4.4 and 4.8). Because of this increase in risk of VTE, thrombosis prophylaxis should be considered for these patients for the period of concomitant chemotherapy.

The use of tamoxifen in combination with anastrozole as adjuvant therapy has not shown improved efficacy compared with tamoxifen alone.

As tamoxifen is metabolised by cytochrome P450 3A4, care is required when co-administering with drugs, such as rifampicin, known to induce this enzyme as tamoxifen levels may be reduced. The clinical relevance of this reduction is unknown.
Pharmacokinetic interaction with CYP2D6 inhibitors, showing a reduction in plasma level of an active tamoxifen metabolite, 4-hydroxy-Ndesmethyltamoxifen (endoxifen), has been reported in the literature. The relevance of this to clinical practice is not known.

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4.6 Fertility, pregnancy and lactation

Pregnancy

Tamoxifen must not be administered during pregnancy. There have been a small number of reports of spontaneous abortions, birth defects and foetal deaths after women have taken tamoxifen, although no causal relationship has been established.

Reproductive toxicology studies in rats, rabbits and monkeys have shown no teratogenic potential.

In rodent models of foetal reproductive tract development, tamoxifen was associated with changes similar to those caused by oestradiol, ethynyloestradiol, clomiphene and diethylstilboestrol (DES). Although the clinical relevance of these changes is unknown, some of them, especially vaginal adenosis, are similar to those seen in young women who were exposed to DES in-utero and who have a 1 in 1000 risk of developing clear-cell carcinoma of the vagina or cervix. Only a small number of pregnant women have been exposed to tamoxifen. Such exposure has not been reported to cause subsequent vaginal adenosis or clear-cell carcinoma of the vagina or cervix in young women exposed in utero to tamoxifen.

Women should be advised not to become pregnant whilst taking tamoxifen and should use barrier or other non-hormonal contraceptive methods if sexually active. Pre-menopausal patients must be carefully examined before treatment to exclude pregnancy. Women should be informed of the potential risks to the foetus, should they become pregnant whilst taking tamoxifen or within two months cessation of therapy.

Breast-feeding

Limited data suggest that tamoxifen and its active metabolites are excreted and accumulate over time in human milk and therefore the drug is not recommended during lactation. The decision either to discontinue nursing or discontinue tamoxifen should take into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Tamoxifen is unlikely to impair the ability of patients to drive or operate machinery. However, fatigue has been reported with the use of Tamoxifen and caution should be observed when driving or operating machinery while such symptoms persist.

4.8 Undesirable effects

Side effects can be classified as either due to the pharmacological action of the drug, e.g. hot flushes, vaginal bleeding, vaginal discharge, pruritus vulvae and tumour flare, or as more general side effects, e.g. gastro-intestinal intolerance, headache, light-headedness and occasionally, fluid retention and alopecia.

When side effects are severe, it may be possible to control them by a simple reduction of dosage (to less than 20mg/day) without loss of control of the disease. If side effects do not respond to this measure, it may be necessary to stop the treatment.

Skin rashes (including isolated reports of erythema multiforme, StevensJohnson syndrome, cutaneous vasculitis and bullous pemphigoid) and commonly hypersensitivity reactions including angiodema have been reported.

Uncommonly, a small number of patients with bony metastases have developed hypercalcaemia on initiation of therapy.

Falls in platelet count, usually to 80,000 to 90,000 per cu mm but occasionally lower, have been reported in patients taking tamoxifen for breast cancer.

A number of cases of visual disturbance including rare reports of corneal changes and common reports of retinopathy have been described in patients receiving tamoxifen. An increased incidence of cataracts has been reported in association with the administration of tamoxifen.

Cases of optic neuropathy and optic neuritis have been reported in patients receiving tamoxifen and, in a small number of cases, blindness has occurred. There is evidence of an increased incidence of ischaemic cerebrovascular events.

Sensory disturbances (including paraesthesia and dysgeusia) have been reported commonly in patients receiving tamoxifen.

Uterine fibroids, endometriosis and other endometrial changes including hyperplasia and polyps have been reported.

Cystic ovarian swellings have occasionally been observed in pre-menopausal women receiving tamoxifen.

Leucopenia has been observed following the administration of tamoxifen, sometimes in association with anaemia and/or thrombocytopenia. Neutropenia has been reported on rare occasions; this can sometimes be severe and very rarely cases of agranulocytosis have been reported.

There is evidence of an increased incidence of ischaemic cerebrovascular events and thromboembolic events including deep vein thrombosis, microvascular thrombosis and pulmonary embolism have been reported commonly during tamoxifen therapy (see sections 4.3, 4.4 and 4.5). When tamoxifen used in combination with cytotoxic agents, there is an increased risk of thrombo-embolic events.
Leg cramps and myalgia have been reported commonly in patients receiving tamoxifen.

Uncommonly, cases of interstitial pneumonitis have been reported.

Tamoxifen has been associated with changes in liver enzyme levels and with a spectrum of more severe liver abnormalities which in some cases were fatal, including fatty liver, cholestasis and hepatitis, liver failure, cirrhosis, and, hepatocellular injury (including hepatic necrosis).

Commonly, elevation of serum trigylceride levels, in some cases with pancreatitis, may be associated with the use of tamoxifen.

Uncommonly incidence of endometrial cancer and rare instances of uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with tamoxifen treatment.

Vaginal polyps have rarely been observed in women receiving tamoxifen

Cutaneous lupus erythematosus has been observed very-rarely in patients receiving tamoxifen.

Porphyria cutanea tarda has been observed very-rarely in patients receiving tamoxifen.

Fatigue has been reported very commonly in patients taking tamoxifen

Unless specified, the following frequency categories were calculated from the number of adverse events reported in a large phase III study conducted in 9366 postmenopausal women patients with operable breast cancer treated for 5 years and unless specified, no account was taken of the frequency within the comparative treatment group or whether the investigator considered it to be related to study medication.

Table 1 Adverse Drug Reactions (ADR) seen with tamoxifen

Frequency	System Organ Class (SOC)	ADR
Very common (≥ 10%)	Gastrointestinal disorders	Nausea
	Metabolism and nutrition	Fluid retention
	Reproductive system and breast	Vaginal bleeding Vaginal discharge
	Skin and subcutaneous tissue	Skin Rash
	Vascular	Hot flushes
	General disorders and administration site conditions	Fatigue
Common ≥ (1% and <10%)	Blood and lymphatic system	Anaemia
	Eye disorders	Cataracts Retinopathy
	Immune system disorders	Hypersensitivity reactions
	Investigations	Elevated triglycerides
	Musculoskeletal and connective tissue	Leg cramp Myalgia
	Neoplasms benign, malignant and unspecified	Uterine fibroids
	Nervous system	Ischaemic cerebrovascular Events Headache Light headedness Sensory disturbanc (including paraesthesia and dysgeusia)

	Reproductive system and breast	Pruritus valvae Endometrial chang (including hyperplasia and polyps)
	Skin and subcutaneous tissue	Alopecia
	Gastrointestinal disorders	Vomiting Diarrhoea Constipation
	Hepatobiliary disorders	Changes in enzymes Fatty liver
	Multiple SOC Terms	Thromboembolic events (including deep ve thrombosis, microvascular thrombosis and pulmonary embolism)
Uncommon ($\geq$ 0.1% and <1%)	Blood and lymphatic system	Thrombocytopenia Leukopenia
	Eye disorders	Visual disturbance
	Gastrointestinal disorders	Pancreatitis
	Metabolism and nutrition	Hypercalcaemia (in patients wit bony metastases)

	Neoplasms benign, malignant and unspecified	Endometrial cancer
	Respiratory,	Interstitial
	thoracic and mediastinal disorders	pneumonitis
	Hepatobiliary disorders	Cirrhosis of the liver

Rare (≥ 0.01% and <0.1%)	Blood and lymphatic system disorders	Neutropenia[a] Agranulocytosis[a]
	Eye disorders	Corneal changes Optic neuropathy[a]
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uterine Sarcoma (mostly malignant mixed Mullerian tumours)[a] Tumour Flare[a]
	Nervous system	Optic neuritis
	Hepatobiliary disorders	Hepatitis Cholestasis[a] Hepatic failure[a] Hepatocellular injury[a] Hepatic necrosis[a]
	Skin and subcutaneous tissue	Angioedema StevenJohnsons syndrome[a] Cutaneous vasculitis[a] Bullous pemphigoid[a] Erythema multiforme[a] Toxic epidermal necrolysis [a]
	Reproductive system and breast disorders	Endometriosis[a] Cystic ovarian swelling[a] Vaginal polyps
	Investigations	Electrocardiogram QT Prolonged.
Very Rare (<0.01%)	Skin and subcutaneous tissue	Cutaneous lupus erythematosus[b]
	Congenital, familial and genetic disorders	Porphyria cutanea tarda[b]

Not known	Skin and subcutaneous tissue disorders	Exacerbation of hereditary angioedema
	Musculoskeletal and connective tissue disorders	Decreased Bone Mineral Density (premenopausal women)

[a] This adverse drug reaction was not reported in the tamoxifen arm (n= 3094) of the above study; however, it has been reported in other trials or from other sources. The frequency has been calculated using the upper limit of the 95% confidence interval for the point estimate (based on 3/X, where X represents the total sample size e.g. 3094). This is calculated as 3/3094 which equates to a frequency category of 'rare'.

[b] The event was not observed in other major clinical studies. The frequency has been calculated using the upper limit of the 95% confidence interval for the point estimate (based on 3/X, where X represents the total sample size of 13,357 patients in the major clinical studies). This is calculated as 3/13,357 which equates to a frequency category of 'very rare'.

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

Overdosage in humans has not been reported. Theoretically an overdosage would be expected to cause enhancement of the anti-oestrogenic side effects as described above. Observations in animals show that extreme overdosage (100-200 times recommended daily dose) may produce oestrogenic effects.

There have been reports in the literature that tamoxifen given at several times the standard dose may be associated with prolongation of the QT interval of the ECG.

No specific treatment for overdosage is known and treatment must be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Estrogens

ATC Code: L02B A01

Pharmacotherapeutic group- Antiestrogens

Tamoxifen is a non-steroidal, triphenylethylene-based drug which displays a complex spectrum of oestrogen antagonist and oestrogen agonist-like pharmacological effects in different tissues. In breast cancer patients, at the tumour level, tamoxifen acts primarily as an antioestrogen, preventing oestrogen binding to the oestrogen receptor. In the clinical situation, it is recognised that tamoxifen leads to reductions in levels of blood total cholesterol and low density lipoproteins in postmenopausal women of the order of 10–20%. Tamoxifen does not adversely affect bone mineral density.

An uncontrolled trial was undertaken in a heterogenous group of 28 girls aged 2 to 10 years with McCune Albright Syndrome (MAS), who received 20 mg once a day for up to 12 months duration. Among the patients who reported vaginal bleeding during the pre-study period, 62% (13 out of 21 patients) reported no bleeding for a 6-month period and 33% (7 out of 21 patients) reported no vaginal bleeding for the duration of the trial. Mean uterine volume increased after 6 months of treatment and doubled at the end of the one-year study. While this finding is in line with the pharmacodynamic properties of tamoxifen, a causal relationship has not been established (see section 4.4). There are no long-term safety data in children. In particular, the long-term effects of tamoxifen on growth, puberty and general development have not been studied.

CYP2D6 polymorphism status may be associated with variability in clinical response to tamoxifen. The poor metaboliser status may be associated with reduced response. The consequences of the findings for the treatment of CYP2D6 poor metabolisers have not been fully elucidated (see sections 4.4, 4.5 and 5.2).

CYP2D6 genotype

Available clinical data suggest that patients, who are homozygote for non-functional CYP2D6 alleles, may experience reduced effect of tamoxifen in the treatment of breast cancer.

The available studies have mainly been performed in postmenopausal women (see sections 4.4 and 5.2).

5.2 Pharmacokinetic properties

Tamoxifen is metabolised mainly in the liver and the peak plasma concentrations after a single dose occur 4 to 7 hours after ingestion. Elimination is accomplished with an initial half-life of 7 to 14 hours but with a long secondary half-life of more than 7 days. The majority of the compound is metabolised to conjugates and hydroxylated derivatives, which are likewise eliminated very slowly. It is excreted slowly in the faeces with only small amounts appearing in the urine.

Tamoxifen is metabolised mainly via CYP3A4 to N-desmethyl-tamoxifen, which is further metabolised by CYP2D6 to another active metabolite endoxifen. In patients who lack the enzyme CYP2D6 endoxifen concentrations are approximately 75% lower than in patients with normal CYP2D6 activity. Administration of strong CYP2D6 inhibitors reduces endoxifen circulating levels to a similar extent.

5.3 Preclinical safety data

Tamoxifen was not mutagenic in a range of in-vitro and in-vivo mutagenicity tests. Tamoxifen was genotoxic in some in-vitro and in-vivo genotoxicity tests in rodents. Gonadal tumours in mice and liver tumours in rats receiving tamoxifen have been reported in long-term studies. The clinical relevance of these findings has not been established.
Tamoxifen is a drug on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Microcrystalline Cellulose
Carmellose Sodium
Povidone
Magnesium Stearate
Potable Water

6.2 Incompatibilities

None stated

6.3 Shelf life

3 years

6.4 Special precautions for storage

Protect from heat. Store in the original package in order to protect from light and moisture

6.5 Nature and contents of container

Aluminium/Aluminium Blister Foils. Dull side laminated to plain 25 micron nylon. Bright side lacquer laminated to 60 micron uPVC.

Pack sizes: 30, 50 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited

11 Boumpoulinas

Nicosia

1060

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8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0216

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 February 1997

10 DATE OF REVISION OF THE TEXT

13/04/2026