1 NAME OF THE MEDICINAL PRODUCT
METOPROLOL TARTRATE TABLETS BP 50mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100mg Metoprolol Tartrate.

Excipient with known effect: Each tablet contains 98.80mg of lactose monohydrate PhEur.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
White to off-white, uncoated tablets.
White to off-white, circular, biconvex uncoated tablets impressed “100” and the identifying letters “MK” on either side of a central division line on one face.

or
White to off-white, circular, biconvex uncoated tablets impressed with the identifying letters “MET” and “100” on either side of a central division line on one face and the Norton logo on the reverse.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4.1 Therapeutic indications
In the management of:
1) Hypertension.
2) Angina pectoris.
3) Cardiac arrhythmias (especially supraventricular tachyarrhythmias).
4) As an adjunctive treatment of thyrotoxicosis.
5) Prophylaxis of migraine.
6) Early intervention of metoprolol tartrate in acute myocardial infarction reduces infarct size and the incidence of ventricular fibrillation. Pain relief may also decrease the need for opiate analgesics.
Metoprolol tartrate has been shown to reduce mortality when administered to patients with acute myocardial infarction.

4.2 Posology and method of administration
Posology
The following dosage regimes are intended only as a guideline and should always be adjusted to the individual requirements of the patient.

Adults
**Hypertension**
Initially 100mg daily. This may be increased, if necessary, to 200mg daily in single or divided doses. Combination therapy with a diuretic or vasodilator may also be considered to further reduce blood pressure. Metoprolol may be administered with benefit both to previously untreated patients with hypertension and to those in whom the response to previous therapy is inadequate. In the latter type of patient the previous therapy may be continued and metoprolol added in to the regime with adjustment of the previous therapy if necessary.

**Angina**
Usually 50-100mg two or three times daily. In general a significant improvement in exercise tolerance and reduction of anginal attacks may be expected with a dose of 50-100mg twice daily.

**Cardiac arrhythmias**
50mg two or three times daily is usually sufficient. If necessary the dose may be increased to 300mg daily in divided doses. Following the treatment of an acute arrhythmia with metoprolol tartrate injection, continuation therapy with metoprolol tablets should be initiated 4-6 hours later. The initial oral dose should not exceed 50mg twice daily.

**Myocardial infarction - early intervention**
In order to achieve optimal benefits from intravenous metoprolol, suitable patients should present within 12 hours of the onset of chest pain. Therapy should commence with 5mg iv every 2 minutes to a maximum of 15mg total as determined by blood pressure and heart rate. The second or third dose should not be given if the systolic blood pressure is less than 90mmHg, the heart rate is less than 40 beats/minute and the P-Q time is greater than 0.26 seconds, or if there is any aggravation of dyspnoea or cold sweating. Orally, therapy should commence 15 minutes after the injection with 50mg every 6 hours for 48 hours. Patients who fail to tolerate the full i.v. dose should be given half the suggested oral dose.

**Maintenance**
The usual maintenance dose is 200mg daily given in divided doses. The treatment should be continued for at least 3 months.

**Thyrotoxicosis**
50mg four times daily. Dose should be reduced as euthyroid state is achieved.

**Prophylaxis of migraine**
100-200mg daily in divided doses (morning and evening).

**Elderly**
There is no evidence to suggest that dosage requirements are different in otherwise healthy elderly patients. However, caution is indicated in elderly patients as an excessive decrease in blood pressure or pulse rate may cause the blood supply to vital organs to fall to inadequate levels. Dosage should be reduced in the elderly where there is impairment of hepatic function.

**Paediatric population**
The safety and efficacy of Metoprolol in children has not been established.

**Renal or Hepatic impairment**
Dosages should be reduced where there is impairment of renal or hepatic function.

**Method of Administration**
For oral administration.

4.3 **Contraindications**

- Known hypersensitivity to metoprolol, related derivatives, any other beta-blockers or to any of the excipients listed in section 6.1.
- Second or third degree atrioventricular block
- Uncontrolled heart failure
- Bradycardia
- Sick-sinus syndrome
- Prinzmetal’s angina
- Untreated phaeochromocytoma
- Metabolic acidosis
- Severe peripheral arterial disease
- Myocardial infarction complicated by significant bradycardia, first degree heart block, systolic hypotension (less than 100mmHg) and/or severe heart failure and cardiogenic shock
- History of bronchospasm and asthma
- Hypotension
- Diabetes if associated with frequent episodes of hypoglycaemia
- Chronic obstructive pulmonary disease
- Renal or hepatic failure
- Therapy resistant hypokalaemia and hyponatraemia, hypercalcaemia, symptomatic hyperuricaemia, anuria.
- Concomitant intravenous administration of calcium blockers of the type verapamil or diltiazem or other antiarrhythmics (such as disopyramide) is contraindicated (exception: intensive care unit).

4.4 **Special Warnings and Precautions for Use**

Abrupt cessation of therapy with a beta-blocker should be avoided especially in patients with ischaemic heart disease. When possible, metoprolol should be withdrawn gradually over a period of 10 days, the doses diminishing to 25mg for the last 6 days. If necessary, at the same time, initiating replacement therapy, to prevent exacerbation of angina pectoris. In addition, hypertension and arrhythmias may develop. When it has been decided to interrupt a beta-blockade in preparation for surgery, therapy should be discontinued for at least 24 hours. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation, however the risk of hypertension may be increased as well. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs. The patient may be protected against vagal reactions by intravenous administration of atropine. During its withdrawal the patient should be kept under close surveillance.

Although cardioselective beta-blockers may have less effect on lung function than non selective beta-blockers these should be avoided in patients with reversible obstructive airways disease unless there are compelling clinical reasons for their use. Although metoprolol has proved safe in a large number of asthmatic patients, it is advisable to exercise care in the treatment of patients with chronic obstructive pulmonary disease.
Therapy with a beta₂-stimulant may become necessary or current therapy require adjustment. Therefore, non-selective beta-blockers should not be used for these patients, and beta₁ selective blockers only with the utmost care. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta-blocker should be gradual.

Simultaneous administration of adrenaline (epinephrine), noradrenaline (norepinephrine) and β blockers may lead to an increase of blood pressure and bradycardia. Metoprolol may induce or aggravate bradycardia, symptoms of peripheral arterial circulatory disorders and anaphylactic shock. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to the bradycardia, the dosage should be reduced.

Metoprolol may be administered when heart failure has been controlled. Digitalisation and/or diuretic therapy should also be considered for patients with a history of heart failure or patients known to have a poor cardiac reserve.

Metoprolol may reduce the effect of diabetes treatment and mask the symptoms of hypoglycaemia. The risk of a carbohydrate metabolism disorder or masking of the symptoms of hypoglycaemia is lower when using metoprolol prolonged-release tablets than when using regular tablet forms for beta₁ selective beta blockers and significantly lower than when using non-selective beta blockers. In labile and insulin-dependent diabetes, it may be necessary to adjust the hypoglycaemic therapy. In case of instable or insulin-dependent diabetes mellitus, it may be necessary to adjust the hypoglycaemic treatment (because of the likelihood of severe hypoglycaemic conditions).

In patients with a phaeochromocytoma, an alpha-blocker should be given concomitantly.

In patients with significant hepatic dysfunction it may be necessary to adjust the dosage because metoprolol undergoes biotransformation in the liver. Patients with hepatic or renal insufficiency may need a lower dosage, and metoprolol is contraindicated in patients with hepatic or renal disease/failure (see section 4.3). The elderly should be treated with caution, starting with a lower dosage but tolerance is usually good in the elderly. It may be necessary to use a lower strength formulation in elderly patients and patients with hepatic or renal impairment and an alternative product should be prescribed.

Patients with anamnestically known psoriasis should take beta-blockers only after careful consideration as the medicine may cause aggravation of psoriasis.

Beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. Adrenaline (epinephrine) treatment does not always give the desired therapeutic effect in individuals receiving beta blockers (see also section 4.5).

Beta-blockers may unmask myasthenia gravis.
In the presence of liver cirrhosis, the bioavailability of metoprolol may be increased, and dosage should be adjusted accordingly.

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

The product labelling will carry the following warning: “Do not take this medicine if you have a history of wheezing or asthma”.

4.5 Interactions with other medicinal products and other forms of interaction

- Anaesthetic drugs may attenuate reflex tachycardia and increase the risk of hypotension. Metoprolol therapy should be reported to the anaesthetist before the administration of a general anaesthetic. If possible, withdrawal of metoprolol should be completed at least 48 hours before anaesthesia. However, for some patients undergoing elective surgery, it may be desirable to employ a beta-blocker as premedication. By shielding the heart against the effect of stress, metoprolol may prevent excessive sympathetic stimulation which is liable to provoke such cardiac disturbance as arrhythmias or acute coronary insufficiency during induction and intubation. Anaesthetic agents causing myocardial depression, such as cyclopropane and trichlorethylene, are best avoided. In a patient under beta-blockade an anaesthetic with as little negative inotropic activity as possible (halothane/nitrous oxide) should be selected.

- It may be necessary to adjust the dose of the hypoglycaemic agent in labile or insulin-dependent diabetes. Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia).

- Digitalis glycosides and/or diuretics should be considered for patients with a previous history of heart failure or in patients known to have a poor cardiac reserve. Digitalis glycosides in association with beta-blockers may increase auriculo-ventricular conduction time.

- As with all beta-blockers particular caution is called for when metoprolol is administered together with prazosin for the first time as the co-administration of metoprolol and prazosin may produce a first dose hypotensive effect.

- Like all beta-blockers, metoprolol should not be given in combination with calcium channel blockers i.e. verapamil and to a lesser extent diltiazem since this may cause bradycardia, hypotension, heart failure and asystole and may increase auriculo-ventricular conduction time. However, combinations of antihypertensive drugs may often be used with benefit to improve control of hypertension. Calcium blockers of the verapamil type should not be administered intravenously to patients receiving beta blockers (see section 4.3).

- Calcium channel blockers (such as dihydropyridine derivatives e.g. nifedipine) should not be given in combination with metoprolol because of the increased risk of hypotension and heart failure. In patients with latent cardiac insufficiency, treatment with beta-blocking agents may lead to cardiac failure. Beta-blockers used in conjunction with clonidine increase the risk of “rebound hypertension”. If combination treatment with clonidine is to be discontinued, metoprolol should be withdrawn several days before clonidine.

- The effects of metoprolol and other antihypertensive drugs on blood pressure are usually additive, and care should be taken to avoid hypotension.
• NSAIDs (especially indometacin) may reduce the antihypertensive effects of beta-blockers possibly by inhibiting renal prostaglandin synthesis and/or causing sodium and fluid retention.

• Care should also be taken when beta-blockers are given in combination with sympathetic ganglion blocking agents, other beta-blockers (i.e. eye drops) or MAO inhibitors. Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines as well as other antihypertensive agents may increase the blood pressure lowering effect.

• Class 1 anti-arrhythmic drugs, e.g. disopyramide, quinidine and amiodarone may have potentiating effects on atrial-conduction time and induce negative inotropic effect. Concurrent use of propafenone may result in significant increases in plasma concentrations and half-life of metoprolol. Plasma propafenone concentrations are unaffected. Dosage reduction of metoprolol may be necessary.

• During concomitant ingestion of alcohol and metoprolol the concentration of blood alcohol may reach higher levels and may decrease more slowly. The concomitant ingestion of alcohol may enhance hypotensive effects.

• The administration of adrenaline (epinephrine) or noradrenaline (norepinephrine) to patients undergoing beta-blockade can result in an increase in blood pressure and bradycardia, although this is less likely to occur with beta1-selective drugs. As beta-blockers may affect the peripheral circulation, care should be exercised when drugs with similar activity eg ergotamine are given concurrently. Concurrent use of moxisylyte may result in possible severe postural hypotension.

• The effect of adrenaline (epinephrine) in the treatment of anaphylactic reactions may be weakened in patients receiving beta blockers (see also section 4.4).

• Metoprolol will antagonise the beta1-effects of sympathomimetic agents but should have little influence on the bronchodilator effects of beta2-agonists at normal therapeutic doses.

• Enzyme inducing agents (e.g rifampicin) may reduce plasma concentrations of metoprolol, whereas enzyme inhibitors (e.g cimetidine, hydralazine and alcohol), selective serotonin reuptake inhibitors (SSRIs) as paroxetine, fluoxetine and sertraline, diphenhydramine, hydroxychloroquine, celecoxib, terbinafine may increase plasma concentrations of hepatically metabolised beta-blockers.

• Metoprolol may impair the elimination of lidocaine.

• Prostaglandin synthetase inhibiting drugs may decrease the hypotensive effects of beta-blockers.

• Cocaine may inhibit the therapeutic effects of beta-blockers and increase the risk of hypertension, excessive bradycardia, and possibly heart block.

• Concurrent use of oestrogens may decrease the antihypertensive effect of beta-blockers because oestrogen-induced fluid retention may lead to increased blood pressure.

• Concurrent use of xanthines, especially aminophylline or theophylline, may result in mutual inhibition of therapeutic effects. Xanthine clearance may also be decreased especially in patients with increased theophylline clearance induced by smoking. Concurrent use requires careful monitoring.

• Concurrent use of aldesleukin may result in an enhanced hypotensive effect.

• Concurrent use of alprostadil may result in an enhanced hypotensive effect.

• There is an increased risk of bradycardia following concomitant use of mefloquine with metoprolol.
• Concomitant use with anxiolytics and hypnotics may result in an enhanced hypotensive effect.
• Concomitant use with corticosteroids may result in antagonism of the hypotensive effect.
• The manufacturer of tropisetron advises caution in concomitant administration due to the risk of ventricular arrhythmias.

4.6 Fertility, pregnancy and lactation

Pregnancy

It is recommended that metoprolol should not be administered during pregnancy or lactation unless it is considered that the benefit outweighs the possible risk to the foetus/infant. Should therapy with metoprolol be employed, special attention should be paid to the foetus, neonate and breast fed infant for any undesirable effects such as slowing of the heart rate. Metoprolol has, however, been used in pregnancy associated hypertension under close supervision after 20 weeks gestation. Although the drug crosses the placental barrier and is present in cord blood no evidence of foetal abnormalities has been reported. However, there is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Beta blockers reduce placental perfusion and may cause foetal death and premature birth. Intrauterine growth retardation has been observed after long-time treatment of pregnant women with mild to moderate hypertension. Beta blockers have been reported to cause bradycardia in the foetus and the newborn child, there are also reports of hypoglycaemia and hypotension in newborn children. Animal experiments have shown neither teratogenic potential nor other adverse events on the embryo and/or foetus relevant to the safety assessment of the product. Treatment with metoprolol should be discontinued 48-72 hours before the calculated birth date. If this is not possible, the newborn child should be monitored for 24-48 hours post partum for signs and symptoms of beta blockade (e.g. cardiac and pulmonary complications).

Lactation

The concentration of metoprolol in breast milk is approximately three times higher than the one in the mother’s plasma. Even though the risk of adverse effects in the breastfeeding baby would appear to be low after administration of therapeutic doses of the medicinal product (except in individuals with poor metabolic capacity) breastfeeding babies should be monitored for signs of beta blockade.

4.7 Effects on ability to drive and use machines

As with all beta-blockers, metoprolol may affect patients’ ability to drive and operate machinery. It should be taken into account that occasionally dizziness or fatigue may occur. Patients should be warned accordingly. These effects may possibly be enhanced in case of concomitant ingestion of alcohol or after changing to another medicinal product.

4.8 Undesirable effects
Frequency estimates: very common ≥10%; common ≥1% and <10%; uncommon ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare < 0.01%.

**Blood and the lymphatic system disorders**  
Very rare: thrombocytopenia

**Psychiatric disorders**  
Rare: depression, nightmares  
Very rare: personality disorder, hallucinations

**Nervous system disorders**  
Common: dizziness, headache  
Rare: alertness decreased, somnolence or insomnia, paraesthesia

**Eye disorders**  
Very rare: visual disturbance (eg. blurred vision), dry eyes and/or eye irritation

**Ear and labyrinth disorders**  
Very rare: tinnitus, and, in doses exceeding those recommended, "hearing disorders (eg. hypoacusis or deafness)

**Cardiac disorders**  
Common: bradycardia  
Rare: heart failure, cardiac arrhythmias, palpitation  
Very rare: cardiac conduction disorders, precordial pain  
Not Known: increase in existing intermittent claudication

**Vascular disorders**  
Common: orthostatic hypotension (occasionally with syncope)  
Rare: oedema, Raynaud’s phenomenon  
Very rare: gangrene in patients with pre-existing severe peripheral circulatory disorders

**Respiratory, thoracic and mediastinal disorders**  
Common: exertional dyspnoea  
Rare: bronchospasm (which may occur in patients without a history of obstructive lung disease)  
Very rare: rhinitis

**Gastrointestinal disorders**  
Common: nausea and vomiting, abdominal pain  
Rare: diarrhoea or constipation  
Very rare: dry mouth  
Not known: retroperitoneal fibrosis (relationship to Metoprolol has not been definitely established), Beta-blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia.

**Hepatobiliary Disorders**  
Not known: hepatitis
Skin and subcutaneous tissue disorders
Rare: skin rash (in the form of urticaria, psoriasiform and dystrophic skin lesions)
Very rare: photosensitivity, hyperhydrosis, alopecia, worsening of psoriasis
Not Known: occurrence of antinuclear antibodies (not associated with SLE)

Musculoskeletal and connective tissue disorders
Rare: muscle cramps
Very rare: arthritis

Reproductive system and breast disorders
Very rare: disturbances of libido and potency
Not known: Peyronie's disease (relationship to Metoprolol has not been definitely established)

General disorders and administration site conditions
Common: fatigue

Investigations
Very rare: weight increase, liver function test abnormal

Post Marketing Experience
The following adverse reactions have been reported during post-approval use of metoprolol: confusional state, an increase in blood triglycerides and a decrease in high density lipoprotein (HDL). Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency.

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; website: www.mhra.gov.uk/yellowcard

4.9 Overdose
Poisoning due to an overdose of metoprolol may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness, coma, nausea, vomiting, cyanosis, hypoglycaemia and, occasionally, hyperkalaemia. The first manifestations usually appear 20 minutes to two hours after drug ingestion.

After ingestion of an overdose or in case of hypersensitivity, the patient should be kept under close supervision and be treated in an intensive-care ward. Absorption of any drug material still present in the gastro-intestinal tract can be prevented by induction of vomiting, gastric lavage, administration of activated charcoal and a laxative. Artificial respiration may be required. Bradycardia or extensive vagal reactions should be treated by administering atropine or methylatropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous
administration of isoprenaline hydrochloride, starting with a dose of approximately 5 micrograms/minute, or dobutamine, starting with a dose of 2.5 micrograms/minute, until required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of 8-10mg glucagon may be considered. If required the injection should be repeated within one hour, to be followed – if required – by an i.v. infusion of glucagon at an administration rate of 1-3mg/hour. Administration of calcium ions, or the use of a cardiac pacemaker may also be considered. In patients intoxicated with hydrophilic beta-blocking agents haemodialysis or haemoperfusion may be considered.

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: Beta blocking agents, selective, ATC code: C07AB02.

Mechanism of action
Metoprolol tartrate is a cardioselective beta-adrenergic blocking agent. It has a relatively greater blocking effect on beta1-receptors (those mediating adrenergic stimulation of heart rate and contractility and release of free fatty acids from fat stores) than on beta2-receptors, which are chiefly involved in broncho-and vasodilation.

5.2 Pharmacokinetic properties

Absorption
Metoprolol is readily and completely absorbed from the gastrointestinal tract.

Distribution
Peak plasma concentrations occur about 1½ hours after a single oral dose. Peak plasma-metoprolol concentrations at steady state with usual doses have been reported as 20-340ng/ml. Metoprolol is widely distributed, it crosses the blood-brain barrier, the placenta. It is slightly bound to plasma protein.

Biotransformation
It is extensively metabolised in the liver; O-dealkylation followed by oxidation and aliphatic hydroxylation. The rate of hydroxylation to alpha-hydroxymetoprolol is reported to be determined by genetic polymorphism; the half-life of metoprolol in fast hydroxylators is stated to be 3-4 hours, whereas in poor hydroxylators it is about 7 hours.

Elimination
The metabolites are excreted in the urine together with only small amounts of unchanged metoprolol. Metoprolol is excreted in breast milk.

Severe angina pectoris
Intrinsic sympathomimetic activity (ISA) may be a disadvantage for the patient with severe angina pectoris. There are however no indications that the efficacy in hypertensives is influenced by this characteristic. In exceptional cases, however, very
high dosages can cause the ISA to predominate over the beta-adrenergic blocking capacity so that restriction of the maximum dosage is indicated.

Respiratory impairment
It has not been proven that beta-blockers with ISA give a lower risk for bronchospasm or enhancement of pre-existing bronchospastic complaints.

5.3 Preclinical safety data
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Also contains:

Silica, colloidal anhydrous
Lactose monohydrate
Magnesium stearate
Maize starch
Cellulose, microcrystalline
Povidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf-life
36 months from the date of manufacture.

Shelf-life after dilution/reconstitution
Not applicable.

Shelf-life after first opening
Not applicable.

6.4 Special precautions for storage

Store below 25°C in a dry place
Protect from light
6.5 Nature and contents of container

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs in cartons:

a) Carton: Printed carton manufactured from white folding box board.

b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-6g/M² PVC and PVdC compatible heat seal lacquer on the reverse side.

Pack sizes: 28s, 30s, 50s, 56s, 60s, 84s, 90s, 100s, 112s, 250s, 500s, 1000s.

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for temporary storage of the finished product before final packaging into the proposed marketing containers. Maximum size of bulk packs: 50,000.

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

Actavis UK Limited
(Trading style: Actavis)
Whiddon Valley
BARNSTAPLE
N Devon EX32 8NS

8 MARKETING AUTHORISATION NUMBER

PL 00142/0383

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 14th February 1994
Date of latest renewal: 26th May 2000
DATE OF REVISION OF THE TEXT

02/12/2016