

## SUMMARY OF PRODUCT CHARACTERISTICS

for

### Paxetin 20mg film-coated tablets

#### 1. NAME OF THE MEDICINAL PRODUCT

Paxetin 20mg film-coated tablets

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Paroxetine 20 mg (as paroxetine hydrochloride, anhydrous 22.2 mg).

For excipients, see 6.1.

#### 3. PHARMACEUTICAL FORM

Film coated tablet.

Round, biconvex, white to off-white film coated tablet, diameter 10 mm, scored on one side and P20 on the other side.

#### 4. CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

Major depressive episode (ICD-10 moderate to severe depressive episode).

Obsessive-compulsive disorder.

Panic disorder with or without agoraphobia.

Social phobia.

##### 4.2 Posology and method of administration

*Depression:* The recommended dosage is 20 mg daily. If necessary, the dose may be increased gradually by 10 mg increments in intervals of at least 2 weeks to a maximum of 50 mg per day according to the patient's response.

*Obsessive compulsive disorder:* The recommended dose is 40 mg daily with an initial dose of 20 mg. If necessary the dose may be increased gradually by 10 mg increments in intervals of at least 2 weeks to a maximum of 60 mg per day according to the patient's response.

*Panic disorder:* The recommended dose is 40 mg daily with an initial dose of 10 mg. If necessary the dose may be increased gradually by 10 mg increments in intervals of at least 2 weeks to a maximum of 50 mg per day according to the patient's response.

A low initial dose is recommended in order to minimise potential aggravation of panic symptoms at the beginning of treatment of panic disorder.

*Social phobia:* The recommended dose is 20 mg daily. If necessary the dose may be increased gradually by 10 mg increments in intervals of at least 2 weeks to a maximum of 50 mg per day according to the patient's response.

It is recommended that paroxetine is administered once daily in the morning with food. The 20 mg tablets should be swallowed whole (or halved) with liquid rather than chewed.

*Renal/hepatic impairment:* Increased plasma concentrations may occur in patients with severe renal impairment (creatinine clearance <30 ml/min) or severe hepatic impairment. For each indication a lower dose than usually recommended must be administered.

#### *General Information*

As with all antidepressant drugs, dosage should be reviewed and adjusted if necessary within two to three weeks of initiation of therapy and thereafter as judged clinically appropriate. Patients should be treated for a sufficient period to ensure that they are free from symptoms. This period should be at least four to six months after recovery (UK guidelines and WHO recommendation) for depression and may be even longer for OCD and panic disorder.

As with many psychoactive medications, abrupt discontinuation should be avoided (see sections 4.4 Special Warnings and Precautions for Use & 4.8 Undesirable Effects) unless the physician determines it is advisable to terminate treatment immediately (e.g. in the case of an adverse event on treatment). The taper phase regimen used in recent clinical trials involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for one week before treatment was stopped. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate, if appropriate, by halving tablets or using the oral suspension.

#### *Special Patient Populations:*

##### *Elderly:*

Increased plasma concentrations of paroxetine occur in elderly subjects. Dosing should commence at the adult starting dose and may be increased weekly in 10 mg increments to a maximum of 40 mg per day according to patient's response.

##### *Children/Adolescents:*

The efficacy and safety of paroxetine in children and adolescents under the age of 18 years have not been established. Controlled clinical studies failed to demonstrate efficacy and do not support the use of Paxetin in the treatment of children and adolescents with Major Depressive Disorder. (See sections 4.3, Contra-indications and 4.8, Undesirable Effects).

Elderly: The recommended initial dose for elderly is the same as for adults. If necessary the dose may be increased gradually by 10 mg increments in intervals of at least 2 weeks to a maximum of 40 mg per day according to the patient's response.

*Duration of treatment:*

Patients should be treated over a period that is sufficient to ensure that they are free of symptoms. This period may be of a duration of several months for depression and possibly longer for obsessive-compulsive conditions and panic disorder. The treatment should be continued for at least 3 months (usually 6 months) according to clinical response.

*Social phobia:*

Placebo controlled clinical studies have shown an effect of paroxetine on this indication at 3 months of treatment. Long-term effect has not been demonstrated.

In order to avoid withdrawal symptoms, the dose should be reduced gradually when the treatment is terminated (see sections 4.4. and 4.8).

### **4.3 Contraindications**

Known hypersensitivity to paroxetine or to any of the excipients.

Paxetin should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder. (See section 4.8, Undesirable Effects).

Monoamine Oxidase Inhibitors – Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA), moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.

Some cases presented with features resembling serotonin syndrome. Symptoms of a drug interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Paxetin should not be used in combination with a MAOI. Paxetin may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 14 days should elapse after discontinuing Paxetin treatment before starting a MAOI or RIMA.

Paxetin should not be used in combination with thioridazine (see Section 4.5, Interactions with other medicinal products and other forms of Interaction).

### **4.4 Special warnings and special precautions for use**

Use of paroxetine together with non-selective irreversible MAO-inhibitors is contraindicated. This combination may lead to severe, sometimes fatal reactions (serotonin-syndrome). Paroxetine must not be used within 2 weeks after discontinuation of treatment with non-selective irreversible MAO-inhibitors. Hereafter the treatment with paroxetine should be initiated with caution and with a gradual increase of the dose until optimal response has been achieved.

Treatment with non-selective irreversible MAO-inhibitors should not be initiated before at least 2 weeks have elapsed after discontinuation of treatment with paroxetine.

Concomitant treatment with A-selective MAO-inhibitors is strongly discouraged and should not be used unless it is absolutely necessary. If these drugs are used concomitantly, special safety measures are requested (e.g. close monitoring of patients, hospitalisation when combination treatment is initiated and initiation of treatment with the lowest recommended doses).

As regards B-selective MAO-inhibitors (selegiline) at recommended doses of paroxetine and selegiline, the risk of serotonin-syndrome is lower than with non-selective MAO-inhibitors and A-selective MAO-inhibitors. Nevertheless, concomitant treatment with selegiline and paroxetine should only be used if it is deemed absolutely necessary, and caution is requested (see also section 4.5).

Paroxetine should not be combined with serotonin precursors (L-tryptophan, oxitriptan) due to the risk of serotonin syndrome (see also section 4.5).

When treating depression there is a suicidal risk especially at the beginning of treatment due to the delay between treatment and clinical improvement. As with all antidepressants the full effect shows possibly earliest after 3 to 4 weeks. A close supervision of the patient is therefore required at the beginning of treatment. Paroxetine should be prescribed with the lowest number of tablets in order to reduce the risk of overdosing.

Withdrawal symptoms have been reported in connection with selective serotonin-reuptake inhibitors (SSRIs). The Symptoms include dizziness, sense disturbances (e.g. paraesthesia), sleep disturbances, headache, nausea, nervousness and increased perspiration. Avoid abrupt discontinuation of treatment.

In some patients a serotonin syndrome, which can be life-threatening, has been seen. The treatment with the drug should be discontinued and supportive measures should be taken.

As with all anti-depressants, paroxetine should be used with caution in patients with a history of mania. Psychoses and mood changes towards manic phase have been reported. This might necessitate withdrawal of treatment.

Paroxetine should be used with caution in patients with epilepsy, or a history of epilepsy or seizures. Paroxetine should be withdrawn if the patient develops epilepsy or convulsions.

In severe hepatic or renal impairment a lower dose than the usually recommended dose should be used. Discontinuation of treatment should be considered if there is a prolonged increase in liver function test results. Caution is advised when treating patients with cardiac conditions.

Hyponatremia has rarely been reported, especially in elderly, and is usually reversible on discontinuation of treatment.

In rare cases paroxetine causes mydriasis and should therefore be used with caution in patients with narrow-angle glaucoma.

There is only limited experience with concomitant treatment with paroxetine and ECT (electro convulsion therapy).

It is suspected that SSRIs, through inhibition of thrombocyte serotonin uptake, may cause an increased bleeding tendency. Caution is advised in patients with previous manifestations of bleeding as well as in concomitant treatment with drugs that may increase the risk of bleeding including anticoagulants and drugs with an effect on thrombocyte function (e.g. non-steroidal anti-inflammatory drugs (NSAID), acetyl salicylic acid, ticlopidine, dipyridamole), since an interaction between these may occur (see section 4.5).

Paroxetine should not be combined with tricyclic antidepressants or other drugs with an influence on the central nervous system, unless this is deemed absolutely necessary (see section 4.5).

Paroxetine should be used with caution in patients on neuroleptic therapy as symptoms of malignant neuroleptic syndrome have been reported.

Paroxetine has not been shown to potentiate the effect of alcohol. As with treatment with other CNS-drugs, alcohol should however be avoided.

Adverse reactions may occur more frequently in concomitant treatment with paroxetine and herbal medicines containing St. John's Wort (*hypericum perforatum*). Paroxetine and drugs containing St. John's Wort should not be taken concomitantly.

Paroxetine is not recommended in children and adolescents below 18 years of age as efficacy and safety have not yet been investigated sufficiently.

Generally all CNS-active drugs should be used with caution in patients with a history of drug abuse since the pharmacological effect that each drug exerts cannot be predicted.

#### **4.5 Interactions with other medicinal products and other forms of interaction**

##### Contraindicated combinations:

Combination with non-selective MAO-inhibitors is contraindicated. It is necessary to keep an interval of 2 weeks from withdrawal of non-selective MAO-inhibitors until initiation of treatment with paroxetine and vice versa.

##### Not recommended combinations:

Concomitant use of A or B-selective MAO-inhibitors is strongly dissuaded and should not be used unless it is deemed absolutely necessary. If the combination is necessary, the clinical monitoring should be intensified (see also section 4.4).

Combination with dextromethorphan should be avoided due to the risk of serotonin syndrome, as dextromethorphan slightly inhibits the uptake of serotonin. Furthermore, both paroxetine and dextromethorphan are metabolised via cytochrome P450 (CYP)2D6, and they therefore may competitively inhibit each other's metabolism.

Other combinations:

There may be a potential pharmacodynamic interaction between paroxetine and oral anticoagulants. Concomitant use of paroxetine and oral anticoagulants may lead to increased anticoagulant activity and risk of bleeding. Therefore paroxetine should be used with special caution in patients in anticoagulant therapy. The INR-level should be controlled more often and if necessary the doses of anticoagulants should be adjusted.

Paroxetine inhibits the CYP2D6 isoenzyme and may therefore inhibit the metabolism of drugs being metabolised by this enzyme, e.g. certain tricyclic antidepressants (clomipramine, desimipramine, nortriptyline, imipramine, amitriptyline), neuroleptics of the phenothiazine type (e.g. perphenazine and thioridazine) as well as type 1C antiarrhythmics (e.g. flecainide, encainide and propafenone) and other SSRI's (e.g. fluoxetine). The use of paroxetine concomitantly with these drugs must be performed with caution.

The metabolism and pharmacokinetics of paroxetine can be influenced by inhibition or induction of drug metabolising enzymes.

Concomitant use of cimetidine and paroxetine may increase the plasma concentrations of paroxetine through inhibition by cimetidine of the CYP-mediated metabolism of paroxetine. Lower doses of paroxetine may be necessary.

Concomitant use of procyclidine and paroxetine may increase the plasma concentration of procyclidine. If anticholinergic effects occur, the dose of procyclidine must be reduced.

As with other SSRIs, concomitant use of paroxetine and serotonergic substances (e.g. MAO-inhibitors, L-tryptophan) may cause serotonin syndrome. The symptoms can be restlessness, confusion, perspiration, hallucinations, hyperreflexia, myoclonus, shiver, tachycardia, tremor, nausea, and diarrhoea.

Concomitant use of triptans (almotriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) increases the risk of hypertension and vasoconstriction of the cardiac artery by adding serotonergic effects.

The risk of use of paroxetine in combination with other CNS-active drugs has not been systematically assessed. Caution is therefore advised if concomitant use is necessary.

Caution is advised in concomitant treatment with paroxetine and lithium due to the risk of mild serotonin syndrome.

NSAIDs, acetylsalicylic acid (see section 4.4).

Adverse reactions can be more frequent in concomitant use of paroxetine and herbal medicines containing St. John's Wort (*hypericum perforatum*) (see section 4.4).

#### **4.6 Use during pregnancy and lactation**

Pregnancy:

Animal studies did not provide any evidence of teratogenicity, however the safety of paroxetine during human pregnancy has not been established. As with all drugs Paxetin should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing foetus.

Lactation:

Paroxetine is known to be excreted in breast milk. Its effects on the nursing infant have not been established. If treatment with Paxetin is considered necessary, discontinuation of breast feeding should be considered.

#### **4.7 Effects on the ability to drive and use machines**

Clinical experience has shown that therapy with paroxetine is not associated with impairment of cognitive or psychomotor function. However, patients should be cautioned about their ability to drive a car and operate machinery.

#### **4.8 Undesirable effects**

*Adverse events reported in adult clinical trials and post marketing use:*

Some of the adverse experiences listed below may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ), rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), including isolated reports. Common and uncommon events were generally determined from pooled safety data from a clinical trial population of >8000 paroxetine-treated patients and are quoted as excess incidence over placebo. Rare and very rare events were generally determined from post-marketing data and refer to reporting rate rather than true frequency.

##### **Blood and lymphatic system disorders:**

Uncommon: abnormal bleeding of the skin (ecchymosis and purpura) and mucous membranes (including gastrointestinal bleeding).

##### **Immune system disorders**

Very rare: allergic reactions (including urticaria and angioedema).

##### **Endocrine disorders**

Very rare: syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

##### **Metabolism & nutrition disorders**

Common: decreased appetite/anorexia.

Rare: hyponatraemia.

Hyponatraemia has been reported predominantly in elderly patients and is sometimes due to the syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

### **Psychiatric disorders (these symptoms may be due to the underlying disease)**

Common: somnolence, insomnia.

Uncommon: confusion, agitation, anxiety, depersonalisation, nervousness.

Rare: manic reactions, hallucinations, panic attacks.

### **Nervous system disorders**

Common: dizziness, tremor.

Uncommon: extrapyramidal disorders.

Rare: convulsions.

Very rare: serotonin syndrome (symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering tachycardia and tremor).

Reports of extrapyramidal disorders including oro-facial dystonia have been received in patients sometimes with underlying movement disorders or who were using neuroleptic medication. In addition, akathisia has been rarely reported (akathisia is characterised by an inability to sit or stand still and subjective complaints of restlessness).

### **Eye disorders**

Common: blurred vision.

Very rare: acute glaucoma.

### **Vascular disorders**

Uncommon: postural hypotension

### **Respiratory, thoracic and mediastinal disorders**

Common: yawning.

### **Gastrointestinal disorders**

Very common: nausea.

Common: constipation, diarrhoea, dry mouth.

Uncommon: vomiting.

### **Hepato-biliary disorders**

Rare: elevation of hepatic enzymes.

Very rare: hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure).

Elevation of hepatic enzymes has been reported. Discontinuation of paroxetine should be considered if there is prolonged elevation of liver function test results.

### **Skin & subcutaneous tissue disorders**

Common: sweating.

Uncommon: skin rashes, pruritus.

Very rare: photosensitivity reactions.

### **Renal & urinary disorders**

Uncommon: urinary retention.

### **Reproductive system & breast disorders**

Very common: sexual dysfunction (including impotence and ejaculation disorders which may be dose related and anorgasmia).

Rare: hyperprolactinaemia / galactorrhoea.

### **Musculoskeletal disorders**

Very rare: arthralgia, myalgia.

### **General disorders & administration site conditions**

Common: asthenia.

### **Symptoms seen on discontinuation of paroxetine treatment:**

Common: Dizziness, sensory disturbances, sleep disturbances, anxiety.

Uncommon: Agitation, nausea, sweating, tremor, confusion.

In common with other selective serotonin reuptake inhibitors, withdrawal symptoms have been reported on stopping treatment (particularly when abrupt). The available evidence does not suggest these are due to dependence. In recent clinical trials which used a taper phase to discontinue treatment with paroxetine (see section 4.2 Posology and Administration) approximately 25% of patients on paroxetine and approximately 15% of patients on placebo experienced such symptoms. That is, approximately 10% of patients in the paroxetine group experienced symptoms potentially attributable to the withdrawal of therapy when corrected for placebo. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion and sweating have been reported. In the majority of patients these events are generally not serious, however, in a small proportion of individuals they may be severe in intensity. These events are generally self limiting and usually resolve within 2 weeks. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering be carried out (see sections 4.2 Posology and Method of Administration and 4.4 Special Warnings and Precautions for Use).

#### *Adverse events from paediatric clinical trials:*

In paediatric clinical trials the following adverse events were reported at a frequency of at least 2% of patients and occurred at a rate of at least twice that of placebo: decreased appetite, tremor, sweating, hyperkinesia, hostility, agitation, emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts and attempted suicide. Suicidal thoughts and suicide attempts were mainly observed in clinical trials of adolescents with Major Depressive Disorder).

In studies that used a tapered withdrawal regimen, symptoms reported during the taper phase or upon discontinuation of paroxetine at a frequency of at least 2% of patients and that occurred at a rate of at least twice that of placebo were: nervousness, dizziness, nausea, emotional lability (including crying, mood

fluctuations, self-harm, suicidal thoughts and attempted suicide) and abdominal pain

#### **4.9 Overdose**

A wide margin of safety is evident from available data.

Experience of paroxetine in overdose has indicated that, in addition to those symptoms mentioned under 'Undesirable Effects', vomiting, dilated pupils, fever, blood pressure changes, headache, involuntary muscle contractions, agitation, anxiety and tachycardia have been reported.

Patients have generally recovered without serious sequelae even when doses of up to 2000 mg have been taken alone. Events such as coma or ECG changes have occasionally been reported, and very rarely a fatal outcome, but generally when paroxetine was taken in conjunction with other psychotropic drugs, with or without alcohol.

No specific antidote is known.

Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Early administration of activated charcoal may delay the absorption of paroxetine.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

ATC-code: N 06 AB 05

Serotonin reuptake inhibitor (antidepressant).

The antidepressant effect of paroxetine is assumed to be related to potentiation of serotonergic activity in the central nervous system as a result of inhibition of the neuronal reuptake of serotonin (5-HT).

Animal studies *in vitro* indicate also that paroxetine is a potent inhibitor and a markedly selective inhibitor of neuronal serotonin re-uptake and has only very weak effects on norepinephrine and dopamine neuronal re-uptake.

#### **5.2 Pharmacokinetic properties**

Paroxetine is almost completely absorbed from the gastrointestinal tract; only 1% of the drug is excreted unchanged with faeces. However, the absolute bioavailability of paroxetine is significantly reduced due to first-pass metabolism. The first-pass effect is reduced with increasing dose which indicates a saturation of first-pass metabolism. The absorption is not influenced by presence of food, milk or antacids. Maximum plasma concentrations ( $t_{max}$ ) are achieved within 2-8 hours, average 6 hours.

Steady-state concentrations of paroxetine are achieved within approximately 1-2 weeks after initiation of treatment. When steady-state has been achieved, there is no further accumulation of the drug.

Paroxetine is distributed in the entire body including central nervous system; only 1% remains in plasma after distribution equilibrium. Binding to proteins is approximately 95%.

Paroxetine is extensively metabolised after oral administration. Paroxetine is mainly metabolised by the polymorph enzyme CYP2D6 and is a potent inhibitor

of this enzyme. The most important metabolites are polar and conjugated oxidation and methylation products which are rapidly excreted. The metabolites are inactive and are mainly excreted via the kidneys (up to 64%). Elimination half-life ( $t_{1/2}$ ) of paroxetine after a single dose of 20 mg is approximately 16-21 hours, while a wider interval of 3-65 hours has been reported in literature.

In elderly, plasma concentrations of paroxetine 2 to 3 times higher compared to adults have been seen. Elderly may show a slower elimination.

Increased plasma concentrations occurred in individuals with renal and hepatic impairment. In severely impaired renal function (creatinine clearance < 30 ml/min) mean AUC and  $C_{max}$  increased to 2.5 and 2.3 times, respectively, the usual concentrations. Patients with moderately impaired renal function (creatinine clearance 30-60 ml/min) showed nearly a doubling of plasma concentrations.

Elimination half-life was significantly prolonged in severe renal impairment (30 hours against 17 hours in control individuals).

In patients with hepatic cirrhosis a doubling of dose-normalised AUC and trough concentrations after 14 days of administration were seen (see section 4.2).

### **5.3 Preclinical safety data**

Conventional studies of genotoxicity and carcinogenicity have not revealed any special hazards to humans.

Phospholipidosis was observed in several organs in toxicity studies with multiple doses in rats, but this was not seen in primates.

Accumulation of phospholipids in laboratory animals was seen after administration of more lipophilic amines. Relevance to humans is unknown.

In reproduction toxicity studies a reduced male fertility and postnatal survival was seen.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

*Tablet core:*

Magnesium stearate  
Sodium starch glycolate (Type A)  
Mannitol  
Microcrystalline cellulose

*Tablet coating:*

Methacrylic acid-methyl methacrylate copolymer (Eudragit E100)  
Polyvinyl alcohol partly hydrolysed  
Titanium dioxide (E 171)  
Talc  
Lecithin soya (E 322)

Xanthan gum (E 415)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

Blister: Keep blister in outer carton

PP container: Store in the original package

**6.5 Nature and contents of container**

Blister strip made of push-through aluminium foil, 20 micron, one side bright, hard, plain, dull side lacquered, bright side heat seal lacquered suitable for sealing against PVC.

Each blister strip contains 10 tablets.

PP-securitainer (white cylindrical container) with a white circular LDPE-cap with desiccant (silica gel).

Pack sizes: 20, 30, 60, 100 film coated tablets.

Not all pack sizes may be marketed.

**6.6 Instructions for use and handling**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

Actavis Ltd.

B16 Bulebel Industrial Estate,

Zejtun ZTN 08

Malta

**8. MARKETING AUTHORISATION NUMBER(S)**

MA245/00201

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

This date will be completed when final marketing authorization is issued.

**10. DATE OF REVISION OF THE TEXT**

24<sup>th</sup> February 2006