Translated by Anne Kræmmer.
Translation of the approved Summary of Product Characteristics on Dosinex tablets (CDS Impluse control disorders)

DANISH MEDICINES AGENCY

30 October 2014

SUMMARY OF PRODUCT CHARACTERISTICS

for

Dostinex, tablets

0. DANISH REGISTER OF PHARMACEUTICAL SPECIALITIES NUMBER
8619

1. NAME OF THE MEDICINAL PRODUCT
Dostinex

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Cabergoline 0.5 mg

Hjælpestoffer, som behandleren skal være opmærksom på:
Dostinex 0,5 mg indeholder 75,9 mg lactose, vandfri.

For excipients, see secion 6.1.

3. PHARMACEUTICAL FORM
Tablets
White flat oblong tablets engraved "PU" on one side and "700" on other side. The tablets are scored.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Inhibition or suppression of lactation. Hyperprolactinemic conditions with amenorrhea, oligomenorrhea, anovulation and galactorrhea. Prolactine producing pituitary tumors. Idiopathic hyperprolactinemia. Empty sella-syndrome with hyperprolactinemia.

4.2 Posology and method of administration
Posology
In general:
In order to avoid gastrointestinal side effects, it is recommended that Dostinex be taken with a meal.

Patients known to be intolerant to dopamine agonists have a reduced risk of side effects if Dostinex treatment is started at reduced doses (e.g. 0.25 mg once a week) followed by the dose being gradually increased until therapeutic dose is reached. If side effects are persistent or severe, temporary reduction of the dosage followed by a gradual increase in dose (e.g. 0.25 mg/week every 14 days) may increase tolerability.

Inhibition of lactation: 1 mg within 24 hours post-partum (see section 4.4).
Suppression of lactation: 0.25 mg twice daily for 2 days.

Hyperprolactinemia:
Initially 0.5 mg weekly, once as a single dose or divided into 2 doses over the week. The dose may be increased with 0.5 mg weekly with a monthly interval until optimal dosage is obtained, depending on serum prolactine and therapeutic effect. Optimal dosage is usually 1 mg weekly, but doses up to 4.5 mg weekly have been used (see section 4.4).

It is recommended that doses higher than 1mg per week are divided into multiple administrations. Patients should be evaluated while the dosage is increased in order to ensure the lowest effective dosage is reached. It is recommended that serum prolactin levels are measured at monthly intervals since serum prolactin usually normalizes within 2 to 4 weeks after the therapeutic dose is reached.

The daily dose must not exceed 3 mg.

After discontinuation of Dostinex, reoccurrence of hyperprolactinaemia usually occurs. However, in some patients a reduced prolactin level has been observed up to several months after discontinuation. In most women, ovulatory cycles persist for at least 6 months after discontinuation of Dostinex.

Patients with severe hepatic insufficiency:
Lower doses of Dostinex should be considered in patients with severe hepatic insufficiency (see section 4.4).

Paediatric population :
Dostinex should not be used in children below 16 years of age due to lack of data on safety and efficacy.

Elderly:
Dostinex has not been formally studied in elderly patients with hyperprolactinemic disorders.

4.3 Contraindications
Hypersensitivity to cabergoline or any of the excipients or any ergot alkaloid.

History of pulmonary, pericardial and retroperitoneal fibrotic disorders (see section 4.4).

Long-term treatment:
Evidence of cardiac valvulopathy as determined by pre-treatment echocardiography. (see section 4.4 Fibrosis and cardiac valvulopathy and related clinical phenomena).

4.4 Special warnings and precautions for use
General:
As with other ergot alkaloids, cabergoline should be given with caution to patients with severe cardiovascular disease, Raynaud's syndrome, peptic ulcer or gastrointestinal bleeding, , or with a history of serious, particularly psychotic, mental disorders.

Contains lactose. Should not be taken by patients with hereditary galactose intolerance, a special form of hereditary lactasedeficiency (Lapp Lactase deficiency) or glucose/galactose malabsorption

Hepatic Insufficiency:

Lower doses should be considered in patients with severe hepatic insufficiency who receive prolonged treatment with Dostinex. Compared to normal volunteers and patients with lesser degrees of hepatic insufficiency, an increase in AUC has been seen in patients with severe hepatic insufficiency (Child-Pugh Class C) who received a single 1 mg dose.

Postural hypotension:
Postural hypotension can occur following administration of cabergoline. Care should be exercised when administering Dostinex concomitantly with other drugs known to lower blood pressure.

Fibrosis and cardiac valvulopathy and related clinical phenomena:
Fibrotic and serosal inflammatory disorders such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, and cardiac valvulopathy involving one or more valves (aortic, mitral and tricuspid) or retroperitoneal fibrosis have occurred after prolonged usage of ergot derivatives with agonist activity at the serotonin $5HT_{2B}$ receptor, such as cabergoline. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of cabergoline.

Erythrocyte sedimentation rate (ESR) has been found to be abnormally increased in association with pleural effusion/fibrosis. Chest x-ray examination is recommended in cases of unexplained ESR increases to abnormal values.

Valvulopathy has been associated with cumulative doses, therefore, patients should be treated with the lowest effective dose. At each visit, the risk-benefit profile of cabergoline treatment for the patient should be reassessed to determine the suitability of continued treatment.

Before initiating long-term treatment:
All patients must undergo a cardiovascular evaluation, including echocardiogram to assess the potential presence of asymptomatic valvular disease. It is also appropriate to perform baseline investigations of ESR or other inflammatory markers, lung function/chest X-ray and renal function prior to initiation of therapy. In patients with valvular regurgitation, it is not known whether cabergoline treatment might worsen the underlying disease. If fibrotic valvular disease is detected, the patient should not be treated with cabergoline (see section 4.3).

During long-term treatment:
Fibrotic disorders can have an insidious onset and patients should be regularly monitored for possible manifestations of progressive fibrosis.

Therefore, during treatment, attention should be paid to the signs and symptoms of:
- Pleuro-pulmonary disease such as dyspnoea, shortness of breath, persistent cough or chest pain
- Renal insufficiency or ureteral/abdominal vascular obstruction that may occur with pain in the loin/flank and lower limb oedema as well as any possible abdominal masses or tenderness that may indicate retroperitoneal fibrosis.
- Cardiac failure: cases of valvular and pericardial fibrosis have often manifested as cardiac failure. Therefore, valvular fibrosis and constrictive pericarditis should be excluded if such symptoms occur.

Clinical diagnostic monitoring for development of fibrotic disorders, as appropriate, is essential. Following treatment initiation, the first echocardiogram must occur within 3-6 months; thereafter, the frequency of echocardiographic monitoring should be determined by

appropriate individual clinical assessment with particular emphasis on the above-mentioned signs and symptoms, but must occur at least every 6 to 12 months.

Cabergoline should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction or valve leaflet thickening (see Section 4.3).

The need for other clinical monitoring (e.g. physical examination including, cardiac auscultation, X-ray, echocardiogram, CT scan) should be determined on an individual basis.

Additional appropriate investigations such as ESR and serum creatinine measurements should be performed if necessary to support a diagnosis of a fibrotic disorder.

Somnolence/Sudden Sleep Onset
Cabergoline has been associated with somnolence and episodes of sudden sleep onset in patients being treated for Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported **infrequently**. Patients should be informed of this, just as they should be advised to be cautious when driving or operating machinery during treatment with cabergoline (see section 4.7). Furthermore, a reduction in dosage or termination of therapy may be considered.

Inhibition/suppression of lactation:
To avoid the increased risk of postural hypotension, single doses of 0.25 mg of Dostinex should not be exceeded in nursing women treated for suppression of established lactation (see section 4.2).

As with other ergot derivatives, Dostinex should not be used in women with preeclampsia or post-partum hypertension unless the potential benefit is judged to outweigh the potential risk.

Treatment of hyperprolactinemic Disorders:
As hyperprolactinemia with amenorrhea/galactorrhea and infertility may be associated with pituitary tumors, the pituitary status should be assessed before treatment with Dostinex is initiated.

Dostinex restores ovulation and fertility in women with hyperprolactinemic hypogonadism.

Before administration of Dostinex, pregnancy should be excluded. Because clinical experience is still limited and the product has a long half-life, as a precautionary measure it is recommended that once regular ovulatory cycles have been achieved women seeking pregnancy discontinue cabergoline one month before intended conception (see section 4.6).

Because pregnancy might occur prior to reinitiation of menses, a pregnancy test is recommended at least every 4 weeks during the amenorrheic period and, once menses are reinitiated, every time a menstrual period is delayed by more than 3 days. Women who wish to avoid pregnancy should be advised to use non-pharmacological contraception during treatment and after discontinuation of treatment until recurrence of anovulation. If pregnancy occurs, discontinuation of treatment with Dostinex should be considered after the benefits and risks for the mother and child are carefully evaluated (see section 4.6). As a precautionary measure, women who become pregnant should be monitored to detect signs of pituitary enlargement since expansion of pre-existing pituitary tumors may occur during pregnancy.

Pathological habit- and impuls act

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, and hypersexuality compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists, including Cabaser dose reduction/tapered discontinuation should be considered if such symptoms develop.

4.5 Interactions with other medicinal products and other forms of interaction

Since cabergoline exerts its therapeutic effect by direct stimulation of dopamine receptors, it should not be concurrently administered with drugs that have dopamine-antagonist activity (such as phenothiazines, butyrophenones, thioxanthenes, metoclopramide) since these might reduce the prolactin-lowering effect of Dostinex.

As with other ergot derivatives, Dostinex should not be used with macrolide antibiotics (e.g. erythromycin) due to increased bioavailability of cabergoline.

Concomitant treatment with other ergot alkaloids during long-term treatment with Dostinex should be avoided until information about possible interactions are available.

4.6 Pregnancy and lactation

There are no adequate and well-controlled studies from the use of cabergoline in pregnant women. Animal studies have not demonstrated teratogenic effects, but reduced fertility and embryo-toxicity were observed in association with pharmacodynamic activity (see section 5.3).

Pregnancy:
Cabergoline should only be used during pregnancy if clearly indicated and after an accurate benefit/risk evaluation.(see section 4.4). Women of childbearing potential should use proper contraceptives during treatment and at least 1 month following discontinuation of treatment.

Only limited data is available on the use of cabergoline during pregnancy, although a dose of 0.5 to 2 mg/week for the treatment of hyperprolactinemic disorders did not appear to be associated with an increased risk of abortion, premature delivery, multiple pregnancy or congenital abnormalities (see section 4.4). Animal studies with cabergoline have not demonstrated teratogenic effects or effects on reproductive performance.

In a twelve year observational study on pregnancy outcomes following cabergoline therapy, information is available on 256 pregnancies. Seventeen of these 256 pregnancies (6.6%) eventuated in major congenital malformations or abortion. Information is available on 23/258 infants who had a total of 27 neonatal abnormalities, both major and minor. Musculoskeletal malformations were the most common neonatal abnormality (10), followed by cardio-pulmonary abnormalities (5). There is no information on perinatal disorders or long-term development of infants exposed to intra-uterine cabergoline. Based on recent published literature, the prevalence of major congenital malformations in the general population has been reported to be 6.9% or greater. Rates of congenital abnormality vary between different populations. It is not possible to accurately determine if there is an increased risk as no control group was included.
Before cabergoline administration, pregnancy should be excluded and after treatment pregnancy should be prevented for at least one month. As cabergoline has an elimination half-life of 79-115 hours in hyperprolactinaemic patients, once regular ovulatory cycles have been achieved women seeking pregnancy should discontinue cabergoline one month before intended conception. This will prevent possible foetal exposure to the drug and will not interfere with the possibility of conception since ovulatory cycles persist in some cases for six months after

cabergoline withdrawal. If conception occurs during therapy, should cabergoline treatment be discontinued as soon as pregnancy is confirmed to limit foetal exposure to the drug (See section 4.4– Treatment of Hyperprolactinemic Disorders)

Breast-feeding:
In rats, cabergoline and its metabolites are excreted in milk.
No studies are available on the excretion of cabergoline in the breast milk in nursing women.
Breast-feeding women should therefore be advised to stop breast-feeding in case of breast-feeding not being stopped or inhibited during treatment.
Since Dostinex inhibits breast-feeding, it should not be used in mothers with hyperprolactinemic disorders who wish to breast-feed their infants.

4.7 Effects on ability to drive and use machines

No label.
Due to side effects, Dostinex can, especially in the beginning of treatment, affect the ability to drive and use machines to a minor or moderate degree.

Due to the risk of drop in blood pressure, patients should exercise caution when driving or during similar activities for the first 4 days of treatment.

Patients being treated with cabergoline and presenting with somnolence and/or sudden sleep onset episodes must be informed to refrain from driving and engaging in activities (e.g. operating machinery) where impaired alertness may put themselves or others at risk of serious injury or death until such adverse reactions have resolved (see section 4.4 Somnolence/Sudden Sleep Onset.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with dostinex with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000).

Immune system disorders Frequency unknown	Hypersensitivity reactions.
Psychiatric disorders Common (≥ 1/100 to < 1/10) Uncommon (≥ 1/1,000 to <1/100) Frequency unknown	Depression. Increased libido, psychotic disorders, aggression, delusions, impulse control disorders such as hypersexuality, pathological gambling,, hallucinations.
Nervous system disorders Very common (≥ 1/10) Common (≥ 1/100 to < 1/10) Uncommon (≥ 1/1,000 to <1/100) Frequency unknown	Dizziness/vertigo*, headache* Somnolence Transient hemianopsia, syncope, marked fatigue during the day as well as episodes of sudden sleep onset, paresthesia Tremor
Eye disorders	Visual impairment

Cardiac disorders Very common (≥ 1/10)	Valvulopathy (including regurgitation) and related conditions (pericarditis and pericardial effusion)
Uncommon (≥ 1/1.000 to <1/100)	Palpitations.
Frequency unknown	Angina pectoris
Vascular disorders Common (≥ 1/100 to < 1/10)	Hot flushes**, a general hypotensive effect in patients on long-term treatment; postural hypotension.
Uncommon (≥ 1/1.000 to <1/100)	Digital vasospasm, fainting.
Respiratory, thoracic and mediastinal disorders Uncommon (≥ 1/1,000 to <1/100)	Pleural effusion, fibrosis (including pulmonary fibrosis, epistaxis, dyspnea.
Very rare (< 1/10,000, including isolated cases)	Pleural fibrosis.
Frequency unknown	Airway disorders, respiratory failure, pleuritis, chest pain
Gastrointestinal disorders Very common (≥ 1/10)	Adominal pain*, dyspepsia, gastritis, nausea*
Common (≥ 1/100 to < 1/10)	Constipation, vomiting**
Rare (≥ 1/10,000 to < 1/1,000)	Epigastric pain
Hepatobiliary disorders Frequency unknown	Abnormal liver function
Skin and subcutaneous tissue disorders Uncommon (≥ 1/1,000 to <1/100)	Dermatological reactions, e.g. acne, pruritus, rash, alopecia.
Musculoskeletal and connective tissue disorders Uncommon (≥ 1/1,000 to <1/100)	Leg cramps
Reproductive system and breast disorders Common (≥ 1/100 to < 1/10)	Mastodynia
General Disorders and administration site conditions Very common (≥ 1/10)	Asthenia***, fatigue
Uncommon (≥ 1/1,000 to <1/100)	Edema, peripheral oedema
Investigations Common (≥ 1/100 to < 1/10)	An asymptomatic fall in blood pressure (≥20 mmHg systolic and 10 mmHg diastolic) usually occurring on day 3-4 post partum
Uncommon (≥ 1/1,000 to <1/100)	A decrease in hemoglobin has been observed in amenhorrheic women during the first few months

	after menses have commenced
Frequency unknown	Elevated serum creatinine phosphokinase., abnormal liver function test

*Very common in patients treated for hyperprolactinaemin disorders; Common in patients treated for inhibition/supression of lactation
** Common in patients treated for hyperprolactinaemin disorders; Uncommon in patients treated for inhibition/supression of lactation
*** Very common in patients treated for hyperprolactinaemin disorders; Uncommon in patients treated for inhibition/supression of lactation

General:
As with other ergot alkaloids, cabergoline may act as a vasoconstrictor and blood circulatory disorders in fingers and toes (digital vasospasm) as well as leg cramps have been observed.

Adverse events are generally dose-related (see section 4.2).

Changes in standard laboratory tests are uncommon during long-term treatment with Dostinex.

Inhibition/Suppression of lactation:
Approximately 14% of women treated in clinical trials with a single 1 mg dose of Dostinex for inhibition of physiologic lactation reported at least one adverse event. Reported adverse events were transient and mild to moderate in severity. The most frequent adverse events were dizziness/vertigo, headache, nausea and abdominal pain. Palpitations, epigastric pain, somnolence (See sections 4.4 and 4.7), epistaxis, and transient hemianopsia were also reported.

Asymptomatic decreases in blood pressure (≥ 20 mmHg systolic and ≥ 10 mmHg diastolic) may occur during the first 3 to 4 days post-partum.

Adverse events have been observed in approximately 14% of nursing women treated with 0.25 mg of DOSTINEX every 12 hours for 2 days for suppression of lactation. Most adverse events were transient and mild to moderate in severity. The most frequent adverse events were dizziness/vertigo, headache, nausea, somnolence (See sections 4.4 and 4.7) and abdominal pain. Vomiting, syncope, asthenia, and hot flushes were also reported.

Hyperprolactinemia:
Data obtained in a controlled clinical trial of 6 months therapy, with doses ranging between 1 and 2 mg per week given in two weekly administrations, indicate a 68% incidence of adverse events during therapy with Dostinex. The adverse events were generally mild to moderate in severity, mainly appearing during the first 2 weeks of therapy. Most disappeared with continued therapy. Severe adverse events were reported at least once during therapy by 14% of patients. Therapy was discontinued because of adverse events in approximately 3% of patients.

Adverse events subsided upon discontinuation of Dostinex, usually within a few days. The most common adverse events reported were: nausea, headache, dizziness/vertigo, abdominal pain/dyspepsia/gastritis, asthenia/fatigue, constipation, vomiting, breast pain, hot flushes, depression and paresthesia.

Pathological habit- and impuls act:

Pathological gambling, increased libido, hypersexuality and compulsive spending or buying, binge eating and compulsive eating, can occur in patients treated with dopamine agonist, inclusive Dostinex.

Reporting adverse events
When a product is approved, is it important that suspected adverse events are reported. This will give a surveillance of the risk/benefit for the product. Physician and health care professionals is asked to report suspected adverse events at www. meldenbivirkning.dk or contact Sundhedsstyrelsen via email at sst@sst.dk or by letter to Sundhedsstyrelsen, Axel Heides Gade 1, 2300 København S.

4.9 Overdose

Symptoms of overdose would likely be those of over-stimulation of dopamine receptors.

Symptoms:
Confusion/psychosis, hallucinations, postural hypotension, nausea and vomiting, and gastric complaints.

Treatment:
Supportive measures should be taken to remove unabsorbed drug and maintain blood pressure, if neccessary.
In addition, the administration of dopamine antagonist drugs may be advisable.

4.10 Dispensing from pharmacy

B (prescription drug)

5. PHARMACOLOGICAL PROPERTIES

5.0 Therapeutic classification

G 02 CB 03 – Other gynecological agents–Prolactin inhibitors

5.1 Pharmacodynamic properties

Dostinex is a synthetic dopaminergic ergoline derivative endowed with a potent and long-lasting prolactin-lowering activity. Cabergoline acts by direct stimulation of the D_2-dopamine receptors on pituitary lactotrophs, thus inhibiting prolactin secretion.

In rats the compound decreases prolactin secretion at oral doses of 3-25 mcg/kg, and *in vitro* at a concentration of 45 pg/ml. In addition, Dostinex exerts a central dopaminergic effect via D_2 receptor stimulation at doses higher than those effective in lowering serum prolactin levels. The long lasting prolactin-lowering effect is probably due to the long persistence of cabergoline in the target organ as suggested by the slow elimination of total radioactivity from the pituitary after a single oral dose in rats (t½ of approximately 60 hours).

The pharmacodynamic effects of Dostinex have been studied in healthy volunteers, puerperal women and hyperprolactinemic patients. After a single oral administration of Dostinex (0.3 - 1.5 mg), a significant decrease in serum prolactin levels was observed in each of the populations studied. The effect is prompt (within 3 hours from administration) and persistent (up to 7 - 28 days in healthy volunteers and hyperprolactinemic patients, and up to 14 - 21 days in puerperal women). The prolactin-lowering effect is dose-related both in terms of degree of effect and duration of action. Because of the long lasting effect, a single dose is usually sufficient to prevent onset of milk secretion.

With regard to the endocrine effects of Dostinex not related to the antiprolactinemic effect, available data from humans confirm the experimental findings in animals indicating that the test compound is endowed with a very selective action with no effect on basal secretion of other pituitary hormones or cortisol. The pharmacodynamic actions of Dostinex not correlated with the therapeutic effect only relate to blood pressure decrease. The maximal hypotensive effect of Dostinex at single doses usually occurs during the first 6 hours after drug intake and is dose-dependent both in terms of maximal decrease and frequency.

5.2 Pharmacokinetic properties

The pharmacokinetic and metabolic profiles of Dostinex have been studied in healthy volunteers of both sexes and in female hyperprolactinemic patients.

After oral administration of the labelled cabergoline, radioactivity was rapidly absorbed from the gastrointestinal tract as the peak of radioactivity in plasma was between 0.5 and 4 hours. Cabergoline is primarily excreted with the bile and ten days after administration about 18% and 72% of the radioactive dose was recovered in urine and feces, respectively. Unchanged drug in urine accounted for 2-3% of the dose.

In urine, the main metabolite identified was 6-allyl-8β-carboxy-ergoline, which accounted for 4-6% of the dose. Three additional metabolites were identified in urine, which accounted overall for less than 3% of the dose. The metabolites have been found to be much less potent than Dostinex in inhibiting prolactin secretion *in vitro*. Dostinex biotransformation was also studied in plasma of healthy male volunteers treated with [^{14}C]-cabergoline: a rapid and extensive biotransformation of cabergoline was shown.

The low urinary excretion of unchanged Dostinex has been confirmed also in studies with non-radioactive product. The half-life of Dostinex, estimated from urinary excretion rates, is long (63-68 hours in healthy volunteers – using a radio-immuno assay, 79-115 hours in hyperprolactinemic patients – using a HPLC method).

On the basis of the half-life, steady state conditions should be achieved after 4 weeks, as confirmed by the mean peak plasma levels of Dostinex obtained after a single dose (37 ± 8 pg/ml) and after a 4-week multiple regimen (101 ± 43 pg/ml). *In vitro* experiments showed that the drug at concentrations of 0.1-10 ng/ml is 41-42% bound to plasma proteins.

Food does not appear to affect absorption and disposition of Dostinex.

5.3 Preclinical safety data

Almost all the findings noted throughout the series of preclinical safety studies are a consequence of the central dopaminergic effects or the long-lasting inhibition of PRL in species (rodents) with a specific hormonal physiology different to man. Preclinical studies of cabergoline indicate a large safety margin for this compound in rodents and in monkeys, as well as a lack of teratogenic, mutagenic or carcinogenic potential.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, anhydrous; Leucin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Tablet glass.

Pack sizes:
0.5 mg tablets: 2 and 8 tablets.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER
Pfizer ApS
Lautrupvang 8
DK-2750 Ballerup

8. MARKETING AUTHORIZATION NUMBER(S)
14398

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28 January 1993

10. DATE OF REVISION OF THE TEXT
30 October 2014