

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ucerax 10mg/5ml Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains 10 mg of hydroxyzine hydrochloride (2mg/ml).

Also contains: sucrose 3.75 mg/5 ml and ethanol 5 mg/5 ml.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Syrup.

Clear, colourless to slightly yellowish syrup with an odour and taste of menthol and hazelnut flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

UCERAX is indicated to assist in the management of anxiety and tension states in adults, psychomotor agitation and acute stress situations such as, for example, those accompanying minor surgical procedures or allergic states.

UCERAX is indicated in the management of pruritus due to allergic conditions such as chronic urticaria and atopic and contact dermatitis, and in histamine-mediated pruritus.

4.2 Posology and method of administration

Posology

Ucerax should be used at the lowest effective dose and for the shortest possible duration.

In adults and children over 40 kg in weight, the maximum daily dose is 100 mg per day.

Anxiety

50 mg/day in 3 separate administrations of 12.5-12.5-25 mg. In more severe cases doses of up to 100 mg/day can be used.

Pruritus

Starting dose of 25 mg before resting, to be followed if necessary with doses up to 25 mg 3 to 4 times daily.

Special populations

The dosage should be adjusted within the recommended dose range, according to patient's response to treatment.

Older People

In the elderly, it is advised to start with half the recommended dose due to a prolonged action. In the elderly, the maximum daily dose is 50 mg per day (see section 4.4).

Patients with hepatic Impairment

In patients with hepatic dysfunction, it is recommended to reduce the daily dose by 33%.

Patients with renal Impairment

Dosage should be reduced in patients with moderate or severe renal function impairment due to decreased excretion of its metabolite cetirizine

Paediatric population (Children from 12 months)

In children up to 40 kg in weight, the maximum daily dose is 2 mg/kg/day.

In children over 40 kg in weight, the maximum daily dose is 100 mg per day.

For symptomatic treatment of pruritus:

- from 12 months: 1 mg/kg/day up to 2 mg/kg/day in divided doses.

4.3 Contraindications

Hypersensitivity to the active substance or to any of its excipients listed in section 6.1, to cetirizine, to other piperazine derivatives, to aminophylline, or to ethylenediamine.

Patients suffering from porphyria.

Patients with pre a known acquired or congenital QT interval prolongation.

Patients with a known risk factor to QT interval prolongation including a known cardiovascular disease, significant electrolytes imbalance (hypokalaemia, hypomagnesaemia), family history of sudden cardiac death, significant bradycardia, concomitant use with drugs known to prolong the QT interval and/or induce Torsade de Pointes (see sections 4.4 and 4.5).

Pregnancy and breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Hydroxyine should be administered cautiously in patients with increased potential for convulsions. Young children are more susceptible to develop adverse events related to the central nervous system (see section 4.8). In children, convulsions have been more frequently reported than in adults.

Because of its potential anticholinergic effects, Hydroxyine should be used cautiously in patients suffering from glaucoma, bladder outflow obstruction, decreased gastro-intestinal motility, myasthenia gravis, or dementia.

Dosage adjustments may be required if Hydroxyine is used simultaneously with other central nervous system depressant drugs or drugs having anticholinergic properties (see section 4.5).

The concomitant use of alcohol and Hydroxyine should be avoided (see section 4.5).

Caution is needed in patients who have a known predisposing factor to cardiac arrhythmia, including electrolytes imbalance (hypokalemia, hypomagnesaemia), who have pre-existing heart disease, or who are concomitantly treated with a potentially arrhythmogenic drug.

In those patients, use of alternative treatments is to be considered.

In the elderly, it is advised to start with half the recommended dose due to a prolonged action (see section 4.2).

Dosage should be reduced in patients with hepatic dysfunction and in patients with moderate or severe renal impairment (see section 4.2).

Cardiovascular effects

Hydroxyzine has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been cases of QT interval prolongation and torsade de pointes in patients taking hydroxyzine. Most of these patients had other risk factors, electrolyte abnormalities and concomitant treatment that may have been contributory (see section 4.8).

Hydroxyzine should be used at the lowest effective dose and for the shortest possible duration.

Treatment with hydroxyzine should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should seek immediate medical attention.

Patients should be advised to promptly report any cardiac symptoms.

Elderly patients

Hydroxyzine is not recommended in elderly patients because of a decrease of hydroxyzine elimination in this population as compared to adults and the greater risk of adverse reactions (e.g. anticholinergic effects) (see sections 4.2 and 4.8).

At a dose higher than 6.5 ml of the 2 mg/ml Ucerax syrup, the sucrose content should be taken into consideration in patients with diabetes mellitus. Sucrose may be harmful to the teeth.

The syrup contains small amounts (0.1 vol %) of ethanol (alcohol). The concentration of alcohol after the administration of 100 ml syrup (equivalent to 200 mg of hydroxyzine) will be up to 100 mg, equivalent to 2 ml beer or 1 ml wine. This has to be taken into account for patient suffering from alcoholism, in pregnant or lactating women, children, and high-risk groups such as patients with liver disease, or epilepsy.

The syrup includes 0.75g of sucrose per ml. Patients with rare hereditary problems of fructose intolerance, glucose-galactose mal-absorption or sucraseisomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Patients should be informed that Hydroxyine may potentiate the effects of CNS depressants or drugs having anticholinergic properties. Dosage should be adapted on an individual basis.

Alcohol also potentiates the effects of Hydroxyine. Hydroxyine antagonizes the effects of betahistine and of anticholinesterase drugs.

The treatment should be stopped at least 5 days before allergy testing or methacholine bronchial challenge, to avoid effects on the test results.

Simultaneous administration of Hydroxyine with monoamine oxidase inhibitors should be avoided.

Hydroxyine counteracts the adrenaline pressor action.

In rats, hydroxyzine antagonised the anticonvulsant action of phenytoin.

Cimetidine 600 mg bid has been shown to increase the serum concentrations of hydroxyzine by 36% and to decrease peak concentrations of the metabolite cetirizine by 20%.

Hydroxyine is an inhibitor of CYP2D6 (K_i : 3.9 μ M ; 1.7 μ g/ml) and may cause at high doses drug-drug interactions with CYP2D6 substrates.

Hydroxyine has no inhibitory effect at 100 μ M on UDP-glucuronyl transferase isoforms 1A1 and 1A6 in human liver microsomes. It inhibits cytochrome P450 2C9/C10, 2C19 and 3A4 isoforms at concentrations (IC_{50} : 103 to 140 μ M ; 46 to 52 μ g/ml) well above peak plasma concentrations. The metabolite cetirizine at 100 μ M has no inhibitory effect on human liver cytochrome P450 (1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4) and UDP-glucuronyl transferase isoforms. Therefore, Ucerax is unlikely to impair the metabolism of drugs which are substrates for these enzymes.

The metabolite cetirizine at 100 μ M has no inhibitory effect on human liver cytochrome P450 (1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4) and UDP-glucuronyl transferase isoforms.

Associations contraindicated

Co-administration of hydroxyzine with drugs known to prolong the QT interval and/or induce Torsade de Pointes e.g. class IA (e.g. quinidine, disopyramide) and III antiarrhythmics (e.g. amiodarone, sotalol), some antihistamines, some antipsychotics (e.g. haloperidol), some antidepressants (e.g. citalopram, escitalopram), some antimalarial drugs (e.g. mefloquine), some antibiotics (e.g. erythromycin, levofloxacin, moxifloxacin), some antifungal agents (e.g. pentamidine), some gastro-intestinal medicines (e.g. prucalopride), some medicines used in cancer (e.g., toremifene, vandetanib), methadone, increase the risk of cardiac arrhythmia. Therefore, the combination is contra-indicated (see section 4.3).

Associations requiring precaution of use

Caution with bradycardia and hypokalaemia-inducing drugs.

Hydroxyzine is metabolized by alcohol dehydrogenase and CYP3A4/5 and an increase in hydroxyzine blood concentrations may be expected when hydroxyzine is co-administered with drugs known to be potent inhibitors of these enzymes.

4.6 Fertility, pregnancy and lactation**Pregnancy**

Animal studies have shown reproductive toxicity. Hydroxyzine crosses the placental barrier leading to higher foetal than maternal concentrations. To date, no relevant epidemiological data are available relating to exposure to Hydroxyzine during pregnancy. Therefore, Hydroxyzine is contra-indicated used during pregnancy.

Labor and delivery

In neonates whose mothers received Hydroxyzine during late pregnancy and/or labour, the following events were observed immediately or only a few hours after birth: hypotonia, movement disorders including extrapyramidal disorders, clonic movements, CNS depression, neonatal hypoxic conditions, or urinary retention.

Breast-feeding

Ucerax is contra-indicated during lactation. Breast-feeding should be stopped if Ucerax therapy is needed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Hydroxyzine may cause tiredness, dizziness, sedation, visual disturbances and thereby may have moderate to major influence, in particular at higher doses and/or if alcohol or sedative drugs are co-administered, on the ability to react and to concentrate. Patients should be warned of this possibility and told that caution is needed if driving a car or operating machinery. Concomitant use of hydroxyzine with alcohol or other sedative drugs should be avoided as it aggravates these effects.

4.8 Undesirable effects***Summary of the safety profile***

Undesirable effects are mainly related to CNS depressant or paradoxical CNS stimulation effects, to anticholinergic activity, or to hypersensitivity reactions.

Tabulated list of adverse reactions

Adverse reactions reported in clinical studies and from post-marketing experience with hydroxyzine are listed in Table 1 below, according to system organ class and per frequency. Frequency categories are defined as follows: Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1000$); Very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions in clinical trials and postmarketing

System Organ Class	Frequency	Adverse Drug Reactions
Immune system disorders	Not known	Hypersensitivity, anaphylactic shock
Psychiatric disorders	Not known	agitation, confusion, disorientation, hallucination
Nervous system disorders	Very common Common Uncommon Not known	somnolence headache dizziness, insomnia, disturbance in attention Tremor, sedation, convulsion, dyskinesia
Eye disorders	Not known	accommodation disorder, vision blurred
Cardiac disorders	Not known	Tachycardia, QT interval prolongation (see section 4.4), ventricular arrhythmias (e.g. Torsade de Pointes)
Vascular disorders	Not known	hypotension
Respiratory, thoracic and mediastinal disorders	Not known	bronchospasm
Gastrointestinal disorders	Common Uncommon Not known	dry mouth Nausea, constipation vomiting
Hepatobiliary disorders	Not known	liver function test abnormal, hepatitis
Skin and subcutaneous tissue disorders	Not known	pruritus, erythematous rash, rash maculo-papular, urticaria, dermatitis, Stevens – Johnson syndrome erythema multiforme, acute generalized exanthematous pustulosis, angioneurotic oedema, fixed drug eruption, sweating increased
Renal and urinary disorders	Not known	urinary retention
General disorders and administration site conditions	Common Uncommon Not known	fatigue asthenia malaise, pyrexia

Description of selected adverse reactions

The following adverse reactions have been observed with cetirizine, the principal metabolite of hydroxyzine: thrombocytopenia, aggression, depression, tic, dystonia, paraesthesia, oculogyric crisis, diarrhea, dysuria, enuresis, asthenia, oedema, weight increased, and could potentially occur with hydroxyzine.

Paediatric population

The paediatric safety profile is in line with the safety profile in adults.

Children are more susceptible to develop adverse events related to the central nervous system including convulsions (see section 4.4). Neonates exposed to hydroxyzine in utero or during labour, are more prone to develop adverse events related to the central nervous system and urinary retention (see section 4.6).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

HPRA Pharmacovigilance

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Website: www.hpra.ie

E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms observed after an important overdose are mainly associated with excessive anticholinergic load, CNS depression or CNS paradoxical stimulation. They include nausea, vomiting, tachycardia, pyrexia, somnolence, impaired papillary reflex, tremor, confusion, or hallucination. This may be followed by depressed level of consciousness, respiratory depression, convulsions, hypotension, or cardiac arrhythmia. Deepening coma and cardiorespiratory collapse may ensue.

Airway, breathing and circulatory status must be closely monitored with continuous ECG recording and an adequate oxygen supply should be available. Cardiac and blood pressure monitoring should be maintained until the patient is free of symptoms for 24 hours. Patients with altered mental status should be checked for simultaneous intake of other drugs or alcohol and should be given oxygen, naloxone, glucose, and thiamine if deemed necessary.

Norepinephrine or metaraminol should be used if vasopressor is needed. Epinephrine should not be used.

Syrup of ipecac should not be administered in symptomatic patients or those who could rapidly become obtunded, comatose or convulsing, as this could lead to aspiration pneumonitis. Gastric lavage with prior endotracheal intubation may be performed if a clinically significant ingestion has occurred.

Activated charcoal may be left in the stomach but there are scant data to support its efficacy. It is doubtful that hemodialysis or hemoperfusion would be of any value. There is no specific antidote.

Literature data indicate that, in the presence of severe, life-threatening, intractable anticholinergic effects unresponsive to other agents, a therapeutic trial dose of physostigmine may be useful. Physostigmine should not be used just to keep the patient awake. If cyclic antidepressants have been congested, use of physostigmine may precipitate seizures and intractable cardiac arrests. Also avoid physostigmine in patients with cardiac conduction defects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hydroxyzine is a psycholeptic and anxiolytic agent (ataractic).

ATC code is N05B B01

The active substance, hydroxyzine dihydrochloride, is a diphenylmethane derivative, chemically unrelated to the phenothiazines, reserpine, meprobamate or benzodiazepines.

Mechanism of action

Hydroxyzine dihydrochloride is not a cortical depressant, but its action may be due to a suppression of activity in certain key regions of the subcortical area of the central nervous system.

Pharmacodynamic effects

Antihistaminic and bronchodilator activities have been demonstrated experimentally and confirmed clinically. An antiemetic effect, both by the apomorphine test and the veriloid test, has been demonstrated.

Pharmacological and clinical studies indicate that hydroxyzine at therapeutic dosage does not increase gastric secretion or acidity and in most cases has mild antisecretory activity. Wheal and flare reduction have been demonstrated in adult healthy volunteers and in children after intradermal injections of histamine or antigens. Hydroxyzine has also revealed its efficacy in relieving pruritus in various forms of urticaria, eczema and dermatitis.

In hepatic function impairment, the antihistaminic effect of one single dose can be prolonged up to 96 hours after intake.

EEG recordings in healthy volunteers show an anxiolytic-sedative profile. Anxiolytic effect was confirmed in patients by the use of various classical psychometric tests. Polysomnographic recordings in anxious and insomniac patients have evidenced an increase in total sleep time, a reduction of total time of night awakenings and a reduction of sleep latency either after single or repeated daily doses of 50 mg. A reduction of the muscular tension was demonstrated in anxious patients at a daily dose of 3 x 50 mg. No memory deficiency has been observed. No withdrawal signs or symptoms have appeared after 4-week treatment in anxious patients.

Onset of action

The antihistaminic effect begins approximately after 1 hour with oral pharmaceutical forms. The sedative effect starts after 5-10 minutes with oral liquid and after 30-45 minutes with tablets. Hydroxyzine has also spasmolytic and sympatolytic effects. It has a weak affinity for muscarinic receptors. Hydroxyzine shows a mild analgesic activity.

5.2 Pharmacokinetic properties

Absorption

Hydroxyzine is rapidly absorbed from the gastro-intestinal tract. The peak plasma level (C_{max}) is reached approximately two hours after oral intake. After single oral doses of 25 mg and 50 mg in adults, C_{max} concentrations are typically 30 and 70 ng/ml, respectively. The rate and extent of exposure to hydroxyzine is very similar when given as tablet or as a syrup. Following repeat administration once a day, concentrations are increased by 30%. The oral bioavailability of hydroxyzine with respect to intramuscular (IM) administration is about 80%. After a single 50 mg IM dose, C_{max} concentrations are typically 65 ng/ml.

Distribution

Hydroxyzine is widely distributed in the body and generally more concentrated in the tissues than in plasma. The apparent volume of distribution is 7 to 16 l/kg in adults. Hydroxyzine enters the skin following oral administration. Skin concentrations of hydroxyzine are higher than serum concentrations, following both single and multiple administration. Hydroxyzine crosses the blood-brain and placental barriers leading to higher fetal than maternal concentrations.

Biotransformation

Hydroxyzine is extensively metabolized. The formation of the major metabolite cetirizine, a carboxylic acid metabolite (approximately 45% of the oral dose), is mediated by alcohol dehydrogenase. This metabolite has significant peripheral H1- antagonist properties. The other metabolites identified include a N-dealkylated metabolite, and an O-dealkylated 1/16 metabolite with a plasma half-life of 59 hours. These pathways are mediated principally by CYP3A4/5.

Elimination

Hydroxyzine half-life in adults is approximately 14 hours (range: 7 - 20 hrs). The apparent total body clearance calculated across studies is 13 ml/min/kg. Only 0.8% of the dose is excreted unchanged in urine. The major metabolite cetirizine is excreted mainly unchanged in urine (25% and 16 % of the hydroxyzine oral and IM dose, respectively).

Special population

Older people

The pharmacokinetics of hydroxyzine was investigated in 9 healthy elderly subjects (69.5 ± 3.7 years) following a single 0.7 mg/kg oral dose. The elimination half-life of hydroxyzine was prolonged to 29 hours and the apparent volume of distribution was increased to 22.5 l/kg. It is recommended to reduce the daily dose of hydroxyzine in elderly patients (see section 4.2).

Paediatric population

The pharmacokinetics of hydroxyzine was evaluated in 12 paediatric patients (6.1 ± 4.6 yrs; 22.0 ± 12.0 kg) following a single oral dose of 0.7 mg/kg. The apparent plasma clearance was approximately 2.5 times that in adults. The half-life was shorter than in adults. It was approximately 4 hours in the 1 year-old patients and 11 hours in the 14 year-old-patients. Dosage should be adjusted in paediatric population (see section 4.2).

Hepatic impairment

In subjects with hepatic dysfunction secondary to primary biliary cirrhosis, total body clearance was approximately 66% that of normal subjects. The half-life was increased to 37 hours and the serum concentrations of the carboxylic metabolite, cetirizine, were higher than in young patients with a normal liver function. Daily dose or dose frequency should be reduced in patients with impaired liver function (see section 4.2).

Renal impairment

The pharmacokinetics of hydroxyzine was studied in 8 severe renally impaired subjects (Creatinine clearance: 24 ± 7 ml/min). The extent of exposure (AUC) to hydroxyzine was not altered in a relevant manner while that to the carboxylic metabolite, cetirizine, was increased. This metabolite is not removed efficiently by hemodialysis. In order to avoid any important accumulation of the cetirizine metabolite following multiple doses of hydroxyzine, the daily dose of hydroxyzine should be reduced in subjects with impaired renal function (see section 4.2).

5.3 Preclinical safety data

The safety pharmacology, acute, sub-acute and chronic toxicity studies did not raise significant safety concerns from data in rodents, dogs and monkeys. Lethal doses 50 (LD50) in rats and mice are respectively 690 and 550 mg/kg per os whereas these are 81 and 56 mg/kg I.V. Single oral doses of 100 mg/kg induced signs of depression, ataxia, convulsions and tremor in dogs. In monkeys, at oral doses exceeding 50 mg/kg, some vomiting occurred, whereas I.V. doses of 15 mg/kg caused convulsions. Intra-arterial injections lead to important tissular lesions in rabbits.

In isolated canine Purkinje fibres hydroxyzine at 3 μ M increased action potential duration suggesting that there was an interaction with potassium channels involved with the repolarisation phase. At a higher concentration, 3 μ M, there was a marked decrease in the action potential duration suggesting a possible interaction with calcium and/or sodium currents. Hydroxyzine produced inhibition of the potassium (IKr) current in human ether α -go-go-related gene (hERG) channels expressed in mammalian cells, with an IC50 of 0.62 μ M, a concentration that is between 10 and 60-fold higher than therapeutic concentrations. Moreover, the hydroxyzine concentrations required to produce effects on cardiac electrophysiology are 10 to 100-fold higher than those required to block H1 and 5-HT2 receptors. In unrestrained conscious dogs monitored by telemetry, hydroxyzine and its enantiomers produced similar cardiovascular profiles though there were some minor differences.

In a first dog telemetry study, hydroxyzine (21 mg/kg po) slightly increased heart rate and shortened PR and QT intervals. There was no effect on QRS and QTc intervals, and thus at normal therapeutic doses, these slight changes are unlikely to be of clinical concern. Similar effects on heart rate and PR interval were observed in a second dog telemetry study, where the absence of effects of hydroxyzine on QTc interval was confirmed up to a single oral dose of 36 mg/kg.

Subacute toxicity was tested in dogs at the dose of 50 mg/kg and caused nausea, trembling and convulsions. Rats survived 30 days with 200 mg/kg/day oral administration of hydroxyzine.

Chronic toxicity was tested in rats at oral doses up to 50 mg/kg without symptoms or histopathological anomalies. Doses of 10 mg/kg reduced the concentration and the viability of spermatocytes. In dogs, oral doses up to 20 mg/kg/day during 6 months were not associated with any symptom or any biological or histopathological anomaly.

Teratogenicity was assessed in pregnant rodents: foetal malformations and foetal abortions were associated with doses over 50 mg/kg of hydroxyzine, this being due to the accumulation of norchlorcyclizine metabolite. Teratogenic doses are much higher than those used in man for therapeutic purpose. No mutagenic activity was shown in the Ames test. A mouse lymphoma study showed marginal increases in mutations of low magnitude in the presence of S9 (i.e. Supernatant fraction obtained from an organ (usually liver) homogenate by centrifuging at 9000 g for 20 minutes in a suitable medium; this fraction contains cytosol and microsomes) at ≥ 15 μ g/mL.

This was close to the maximum level of toxicity for this study. A study for micronuclei induction in rats was negative. As only very marginal effects were noted in the in vitro study and the in vivo study was negative, it is considered that hydroxyzine is not a mutagen.

Animal carcinogenicity studies have not been undertaken with hydroxyzine. However, the drug is not mutagenic and has not been associated with any overt increased tumourgenic risk during several decades of clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Ethanol
Sodium benzoate (E211)
Levomenthol
Imitation Hazelnut flavour
Purified water

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

The syrup is filled in an 200ml amber glass bottle (type III - Ph. Eur.) closed by a polypropylene child-proof screw cap equipped with a polyethylene inner joint.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA0891/005/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th July 1991

Date of last renewal: 26th July 2006

10 DATE OF REVISION OF THE TEXT

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