SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Serenace 500mcg Capsules

Haloperidol Capsules BP 500mcg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Haloperidol BP 0.5mg

3 PHARMACEUTICAL FORM

Hard gelatin capsule for oral administration

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Psychotic disorders- schizophrenia, mania and hypomania, especially paranoid psychoses.

Mental or behavioural problems such as aggression, hyperactivity and self-mutilation in the mentally retarded.

Moderate to severe psychomotor agitation, excitement, violent or dangerously impulsive behaviour.

Gilles de la Tourette syndrome and severe tics.

Childhood behaviour disorders, especially when associated with hyperactivity and aggression.

Restlessness and agitation in the elderly.

Nausea and vomiting.

Adjunct to short-term management of anxiety.

4.2 Posology and method of administration

There is considerable variation from patient to patient in the response to treatment and the dosage required. As with all antipsychotics, dosage should be individualised according to the needs and response of each patient.

To determine the initial dosage, consideration should be given to the patient's age, severity of symptoms and previous response to other antipsychotic therapy. Oral dosage may be given in single or divided doses. Administration twice daily is sufficient in most cases.

Adults
Psychotic behaviour; Mental or behavioural problems; Moderate to severe psychomotor agitation or impulsive behaviour.

Initial treatment
Initial dosage may range from as little as 1.5mg daily to 20mg daily, dependent on the characteristics, severity of symptoms and response of each individual patient. It may be necessary to increase the dosage gradually to obtain maximum control of symptoms. In severely disturbed or resistant patients, the maximum daily dose recommended is 30mg.

Maintenance treatment
Once a satisfactory therapeutic response has been achieved, dosage should be reduced gradually to the lowest effective maintenance level which is often as low as 3 to 10mg daily dependent on the characteristics and response of each individual patient.

Gilles de la Tourette syndrome
Initial dosage is usually 2mg daily. During the acute phase of treatment, dosage can be increased gradually to obtain maximum control of symptoms and may range between 6 and 30mg daily.

Once a satisfactory therapeutic response has been achieved, dosage should be reduced gradually to the lowest effective maintenance level which for most patients is 4mg daily.

Nausea and vomiting
1mg daily orally has proved useful.

Anxiety
500 mcg twice daily.

Elderly
Half the recommended adult starting dose may be sufficient for therapeutic response in the elderly. The maximum and maintenance dose will generally be lower for debilitated or geriatric patients who may be more sensitive to Serenace.

Children (Oral administration)
25 to 50 micrograms per Kg body weight per day to a maximum of 10mg, although, exceptionally, adolescents may require up to 30mg daily.

Route of administration
Oral.

4.3 Contraindications

Comatose states, CNS depression, lesions of basal ganglia, patients with Parkinson's disease or known hypersensitivity to haloperidol or to any of the excipients and use during lactation.

In common with other neuroleptics, haloperidol has the potential to cause rare prolongation of the QT interval. Use of haloperidol is therefore contra-indicated in patients with clinically significant cardiac disorders (e.g. recent acute myocardial infarction, uncompensated heart failure, arrhythmias treated with class IA and III antiarrhythmic medicinal products), QTc interval prolongation, history of ventricular arrhythmia or Torsades de pointes, clinical significant bradycardia, second and third degree heart block and uncorrected hypokalaemia. Haloperidol should not be used concomitantly with other QT prolonging drugs (see section 4.5).

4.4 Special warnings and precautions for use

Cases of sudden death have been reported in psychiatric patients receiving anti-psychotic drugs, including haloperidol.

Increased Mortality in Elderly people with Dementia
Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Haloperidol is not licensed for the treatment of dementia-related behavioural disturbances.

Cardiovascular effects
Very rare reports of QT prolongation and/or ventricular arrhythmias, in addition
to rare reports of sudden death, have been reported with haloperidol. They may occur more frequently with high doses and in predisposed patients.

The risk-benefit of haloperidol treatment should be fully assessed before treatment is commenced and patients with risk factors for ventricular arrhythmias such as cardiac disease, family history of sudden death and/or QT prolongation; uncorrected electrolyte disturbances; subarachnoid haemorrhage; starvation; alcohol abuse or those receiving concomitant therapy with other drugs known to prolong the QT interval, should be monitored carefully (ECGs and potassium levels), particularly during the initial phase of treatment, to obtain steady plasma levels. The risk of QT prolongation and/or ventricular arrhythmias may be increased with higher doses (see Sections 4.8

and 4.9) or with parenteral use, particularly intravenous administration. ECG monitoring should be performed for QT prolongation and for serious cardiac dysrhythmias if haloperidol is administered intravenously.

Haloperidol should be used with caution in patients known to be slow metabolisers of CYP2D6, and during use of cytochrome P450 inhibitors. Concomitant use of antipsychotics should be avoided. (See Section 4.5)

A baseline ECG is recommended prior to treatment in all patients (see section 4.3 Contraindications), especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination. During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual patient basis. Whilst on therapy, the dose should be reduced if QT is prolonged and discontinued if QTc is >500ms.

Periodic electrolyte monitoring is recommended, particularly if on diuretics or during inter-current illness.

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Haloperidol should be used with caution in patients with risk factors for stroke.

Neuroleptic malignant syndrome
In common with other antipsychotic drugs, haloperidol has been associated with neuroleptic malignant syndrome (NMS). An idiosyncratic response characterised by hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness, coma and elevated CPK. Signs of autonomic dysfunction such as tachycardia, labile arterial pressure and sweating may precede the onset of hyperthermia, acting as early warning signs. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Tardive dyskinesia
As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long term therapy or after drug discontinuation. The syndrome is mainly characterised by rhythmical involuntary movements of the tongue, face, mouth or jaw.

The manifestations may be permanent in some patients. The syndrome may be masked when treatment is reinstituted, when the dosage is increased or when a switch is made to a different antipsychotic drug. Treatment should be discontinued as soon as possible.

Extrapyramidal symptoms
In common with all neuroleptics, extrapyramidal symptoms may occur, e.g. tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia.

Anti-parkinson drugs of the anticholinergic type may be prescribed as required, but should not be prescribed routinely as a preventive measure..If concomitant anti-parkinson medication is required, it may have to be continued after stopping haloperidol if its excretion is faster than that of Haloperidol in order to avoid the development or aggravation of extrapyramidal symptoms. The physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including anti Parkinson agents, are administered concomitantly with Haloperidol.

Seizures/Convulsions
It has been reported that seizures can be triggered by Haldol. Caution is advised in patients suffering from epilepsy and in conditions predisposing to convulsions (e.g., alcohol withdrawal and brain damage).

Hepatobiliary concerns
As Haloperidol is metabolised by the liver, caution is advised in patients with liver disease. Isolated cases of liver function abnormalities or hepatitis, most often cholestatic, have been reported.

Endocrine system concerns
Thyroxin may facilitate Haloperidol toxicity. Antipsychotic therapy in patients with hyperthyroidism should be used only with great caution and must always be accompanied by therapy to achieve a euthyroid state.

Hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligo- or amenorrhoea. Very rare cases of hypoglycaemia and of syndrome of Inappropriate ADH secretion have been reported.

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with haloperidol and preventive measures undertaken.

Additional considerations

In schizophrenia, the response to anti-psychotic drug treatment may be delayed. Also, If drugs are withdrawn, recurrence of symptoms may become apparent for several weeks and months. Acute withdrawal symptoms including nausea, vomiting, sweating and insomnia have been described after abrupt cessation of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

As with all anti-psychotic agents, haloperidol should not be used alone where depression is predominant. It may be combined with antidepressant to treat those conditions in which depression and psychosis coexist. Haloperidol may impair the metabolism of tricyclic antidepressant (clinical significance).

Caution is advised in patients with renal failure and phaeochromocytoma.

Administer with care to patients with severe cardiovascular disorders, because of the possibility of transient hypotension. Should hypotension occur and a vasopressor be required, adrenaline should not be used since haloperidol may block its vasopressor activity and further lowering of the blood pressure may occur.

Use cautiously in thyrotoxic patients and those with arteriosclerosis who may have occult or manifest lesions of the basal ganglia. Such patients may be more prone to develop extrapyramidal symptoms.

Concomitant use of haloperidol with other neuroleptics should be avoided.

Paediatric population
Available safety data in the paediatric population indicate a risk of Extrapyramidal symptoms, including tardive dyskinesia, and sedation. No long-term safety data are available.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use of Haloperidol with drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias, including torsade de pointes. Therefore concomitant use of these drugs is not recommended (see section 4.3).

Haloperidol may have a synergistic effect with other QT prolonging drugs and therefore co-administration should be avoided. Examples include certain Class IA and III antiarrhythmics, (such as quinidine, disopyramide, procainamide, amiodarone, sotalol and dofetilide), certain antimicrobials (such as sparfloxacin, moxifloxacin and erythromycin IV), tricyclic antidepressants (e.g. amitriptyline), tetracyclic antidepressants (e.g. maprotiline), other neuroleptics (e.g. phenothiazines, pimozide, and sertindole), antihistamines (e.g. terfenadine), cisapride, bretylium and antimalarials (e.g. quinine and mefloquine). This list in not comprehensive.

Concurrent use of drugs causing electrolyte imbalance may increase the risk of ventricular arrhythmias and is not recommended (see section 4.4). Diuretics, in particular those causing hypokalaemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred.

Haloperidol is metabolised by several routes, including glucuronidation and the cytochrome P450 enzyme system (particularly CYP 3A4 or CYP 2D6). Inhibition of these routes of metabolism by another drug or a decrease in CYP 2D6 enzyme activity may result in increased haloperidol concentrations and an increased risk of adverse events, including QT-prolongation. In

pharmacokinetic studies, mild to moderately increased haloperidol concentrations have been reported when haloperidol was given concomitantly with drugs characterised as substrates or inhibitors of CYP 3A4 or CYP 2D6 isozymes, such as, itraconazole, buspirone, venlafaxine, alprazolam, fluvoxamine, quinidine, fluoxetine, sertraline, chlorpromazine, and promethazine. A decrease in CYP2D6 enzyme activity may result in increased haloperidol concentrations. Increases in QTc and extrapyramidal symptoms have been observed when haloperidol was given with a combination of the metabolic inhibitors ketoconazole (400 mg/day) and paroxetine (20 mg/day). It may be necessary to reduce the haloperidol dosage. Haloperidol plasma levels should therefore be monitored and reduced if necessary.

Effects of other drugs on Haloperidol

When prolonged treatment with enzyme-inducing drugs such as carbamazepine, phenobarbital, rifampicin is added to haloperidol therapy, this results in a significant reduction of haloperidol plasma levels. Therefore during combination treatment, Haloperidol dose should be adjusted, when necessary. After stopping this drug, it may necessary to reduce the dosage of Haloperidol.

Sodium valproate, a drug known to inhibit glucuronidation, does not affect haloperidol plasma levels.

Effects of Haloperidol on other drugs

In common with all neuroleptics, Haloperidol may potentiate the central nervous system depression produced by other CNS-depressant drugs including alcohol, hypnotics, sedatives or strong analgesics. Enhanced CNS effects (sedation, mental disturbances) have been reported with the combined use of methyldopa and haloperidol. Severe neuromuscular symptoms with impairment of consciousness and fever have been reported with combined use of lithium and haloperidol. A causal relationship has not been established. However, patients receiving such combined therapy should be carefully observed for early evidence of neurological toxicity and treatment should be discontinued if such signs appear.

Haloperidol may antagonise the action of adrenaline and other sympathomimetic agents and reverse the blood-pressure lowering effects of adrenergic-blocking agents such as guanethidine.

Haloperidol may impair the anti-parkinson effects of levodopa.

Haloperidol inhibits the metabolism of tricyclic antidepressants thereby increasing plasma levels of these drugs.

Other forms of interaction
In rare cases, an encephalopathy-like syndrome has been reported in combination with lithium and haloperidol. It remains controversial whether these cases represent a distinct clinical entity, or whether they are in fact cases

of NMS and/or lithium toxicity. Signs of encephalopathy-like syndrome include confusion, disorientation, headache, disturbances of balance and drowsiness. One report showing symptom less EEG abnormalities on the combination has suggested that EEG monitoring might be advisable. When lithium and haloperidol therapy are used concomitantly, haloperidol should be given in the lowest effective dose and lithium level should be monitored and kept below 1 mm/L. If symptoms of encephalopathy-like syndrome occur, therapy should be stopped immediately.

Antagonism of the effect of the anticoagulant phenindione has been reported.

The dosage of anticonvulsants may need to be increased to take account of the lowered seizure threshold.

Co-administration of indometacin with haloperidol could cause severe drowsiness and confusion.

4.6 Pregnancy and lactation

Pregnancy: The safety of Serenace in pregnancy has not been established. There is some evidence of harmful effects in some, but not all animal studies. Reproduction studies in rodents have shown an increased incidence of resorption, reduced fertility and pup mortality. No specific teratogenic effect has been reported in rats, rabbits or dogs but cleft palate and open eye syndrome have been observed in mice.

No well-controlled studies of haloperidol use in pregnant women have been conducted. Two cases of foetal limb malformation have been reported following maternal use of haloperidol, combined with other drugs during the first trimester. Neonates exposed to antipsychotics (including Serenace) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. No causal relationship has been established. Use of haloperidol during pregnancy requires that the anticipated benefit be weighed against the possible hazards to mother and foetus.

Lactation: Haloperidol has been detected in breast milk. There have been isolated cases of extrapyramidal symptoms in breast-fed children. If use of haloperidol is considered essential, breast feeding should be discontinued.

4.7 Effects on ability to drive and use machines

Some degree of sedation or impairment of alertness may occur, particularly with higher doses, especially at the start of treatment. These effects may be potentiated by alcohol or other CNS depressants. Patients should be warned of the risks of sedation and advised not to drive or operate machinery during treatment, until their susceptibility is known.

4.8 Undesirable effects

The data provided below covers all haloperidol formulations including the Haloperidol Decanoate formulations.

The safety of Haloperidol was evaluated in 284 haloperidol-treated subjects who participated in 3 placebo-controlled, and in 1295 haloperidol-treated subjects who participated in sixteen double-blind active comparator-controlled clinical trials. The safety of Haloperidol decanoate was evaluated in 410 subjects who participated in 3 comparator trials (one comparing haloperidol vs. fluphenazine and two comparing the decanoate formulation to the oral formulation), 9 open label trials and 1 dose responsive trial. Based on pooled safety data from these clinical trials, the most commonly reported (% incidence) Adverse Drug Reactions (ADRs) were: Extrapyramidal disorder (34), Insomnia (19), Agitation (15), Hyperkinesia (13), Headache (12), Psychotic disorder (9), Depression (8), Weight increased (8), Orthostatic hypotension (7) and Somnolence (5).

Including the above mentioned ADRs, the following ADRs have been observed from clinical trials and post-marketing experiences reported with the use of Haloperidol and Haloperidol Decanoate. Frequencies displayed use the following convention:

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), not known (cannot be estimated form the available data).

Blood and lymphatic system disorders
Uncommon: Leukopenia
Not Known: Agranulocytosis; Neutropenia; Pancytopenia; Thrombocytopenia

Immune system disorders
Uncommon: Hypersensitivity
Not known: Anaphylactic reaction

Endocrine disorders
Rare: Hyperprolactinaemia
Not known: Inappropriate anti-diuretic hormone secretion

Metabolism and nutrition disorders
Not known: Hypoglycaemia

Psychiatric disorders
Very common: Agitation; Insomnia
Common: Depression; Psychotic disorder
Uncommon: confusional states; Libido Decreased; Loss of libido; Restlessness

Nervous system disorders
Very common: Extrapyramidal disorder; Hyperkinesia; Headache

Common: Tardive dyskinesia; Oculogyric Crisis; Dystonia; Dyskinesia; Akathisia; Bradykinesia; Hypokinesia; Hypertonia; Somnolence; Masked Faces, Tremor; Dizziness
Uncommon: Convulsion; Parkinsonism; Akinesia; Cogwheel rigidity; Sedation; Muscle Contractions Involuntary
Rare: Motor dysfunction; Neuroleptic malignant syndrome; Nystagmus;
Not known: Drowsiness, Dystonia producing laryngeal/pharyngeal spasm associated with cyanosis, gagging, respiratory distress and asphyxia

Eye Disorders
Common: Visual disturbance
Uncommon: Vision blurred

Ear and labyrinth disorders
Not Known: vertigo

Cardiac disorders
Uncommon: Tachycardia
Not known: Ventricular Fibrillation; Torsade de pointes; Ventricular Tachycardia; Extrasystoles

Vascular disorders
Common: Orthostatic Hypotension; Hypotension

Respiratory, Thoracic and mediastinal
Uncommon: Dyspnoea
Rare: Bronchospasm
Not known: Laryngeal Oedema; Laryngospasm

Gastrointestinal disorders
Common: Constipation; Dry mouth; salivary hypersecretion; Nausea; Vomiting
Not known:, Loss of appetite; Dyspepsia

Hepatobiliary disorders
Common: Liver function test abnormal
Uncommon: Hepatitis; Jaundice
Not known: Acute Hepatic Failure; Cholestasis; transient abnormalities of liver function in the absence of jaundice

Skin and subcutaneous tissue disorders
Common: Rash
Uncommon: Photosensitivity Reaction; Urticaria; Pruritis; Hyperhidrosis
Not known: Leukocytoclastic Vasculitis; Dermatitis Exfoliative and erythema multiforme

Musculoskeletal and connective tissue disorders
Uncommon: Torticollis; Muscle rigidity; Muscle Spasms; Musculoskeletal stiffness
Rare: Trismus: Muscle Twitching

Renal and urinary disorders
Common: Urinary retention

Pregnancy, puerperium and perinatal conditions
Not Known: Drug withdrawal syndrome neonatal (see 4.6)

Reproductive system and breast disorders
Common: Erectile dysfunction
Uncommon: Amenorrhoea; Dysmenorrhoea; Galactorrhoea; Breast discomfort; Breast Pain;
Rare: Menorrhagia; Menstrual Disorder; Sexual Dysfunction
Not known: Gynaecomastia, Priapism

General disorders and administration site conditions
Uncommon: Gait disturbance; Hyperthermia; Oedema
Not known: Sudden Death; Face Oedema; Hypothermia

Investigations
Common: Weight increased; Weight decreased
Rare: Electrocardiogram QT prolonged

Additional Information

Cardiac effects such as QT-interval prolongation, torsade de pointes, ventricular arrhythmias, including ventricular fibrillation and ventricular tachycardia), and cardiac arrest have been reported. These effects may occur more frequently with high doses, and in predisposed patients (see 4.4 Special Warnings and Precautions for Use).

Toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported in patients taking haloperidol. The true incidence of these reports in not known.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs- Frequency unknown.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Intensification of the known pharmacological and adverse effects may occur. The most prominent would be severe extrapyramidal symptoms, hypotension or sedation. The risk of ventricular arrhythmias possibly associated with QT-prolongation should be considered. The patient may appear comatose with respiratory depression and hypotension which could be severe enough to

produce a shock-like state. Paradoxically hypertension rather than hypotension may occur. Convulsions may also occur.

Extrapyramidal reactions may include muscular weakness or rigidity and a generalised or localised tremor. With accidental overdosage hypothermia, bradycardia, sinus arrhythmia and hypertension have been reported in young children.

Treatment
No specific antidote has been identified.

In the event of overdosage the stomach should be emptied by aspiration and lavage. Emetics should not be used. Establishment of patent airway and artificial ventilation may be needed. In view of isolated reports of arrhythmia ECG monitoring is strongly advised. Hypotension may be counteracted by placing the patient in the head-down position and by the use of a plasma expander and careful use of a vasopressor agent such as noradrenaline. Adrenaline should not be used. The patient should be monitored carefully for 24 hours or longer, body temperature and adequate fluid intake should be maintained. Severe extrapyramidal reactions should be treated with parenteral antihistamines or antiparkinsonian drugs. The relatively long plasma elimination half-life of haloperidol should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Haloperidol is a butyrophenone. Its pharmacological profile of activity includes a pronounced capacity to induce extrapyramidal reactions and a low incidence of autonomic side-effects, such as hypotension.

5.2 Pharmacokinetic properties

The pharmacokinetics of haloperidol have been studied in healthy volunteers and patients. In volunteers, following a single intravenous or oral dose, serum elimination half-life ranged from 10-19 hours and 12-38 hours respectively. Similar elimination half-lives were observed in patients after administration of a single oral or intramuscular dose of the drug or after withdrawal of the drug from patients who were in a steady state. Steady state serum levels were usually achieved within 6 days on a fixed oral dosage.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Ph.Eur.
Corn Starch Ph.Eur.

Hard Gelatin Capsule Shell:
Tartrazine (E102)
Patent Blue V (E131)
Titanium Dioxide (E171)

Printing ink:
Shellac
Black iron oxide (E172)
Propylene glycol (E1520)

6.2 Incompatibilities

None.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in a dry place below 30°C.

6.5 Nature and contents of container

High density polyethylene bottles with tamper-evident snap closure, or amber glass bottles with metal screw cap in pack sizes of 7, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100,112, 120, 250, 1000 and 5000. PVC/Aluminium blisters, or PVDC coated PVC/aluminium blisters in pack sizes of 7, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 112 and 120.

6.6 Special precautions for disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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