

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sotalol Hydrochloride 80 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80mg sotalol hydrochloride

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Tablet

White to off white, round, biconvex, uncoated tablets debossed with 'DR' on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sotalol is indicated for:

Ventricular arrhythmias:

- Treatment of life-threatening ventricular tachyarrhythmias;
- Treatment of symptomatic non-sustained ventricular tachyarrhythmias;

Supraventricular arrhythmias:

- Prophylaxis of paroxysmal atrial tachycardia, paroxysmal atrial fibrillation, paroxysmal A-V nodal re-entrant tachycardia, paroxysmal A-V re-entrant tachycardia using accessory pathways, and paroxysmal supraventricular tachycardia after cardiac surgery;
- Maintenance of normal sinus rhythm following conversion of atrial fibrillation or atrial flutter.

4.2 Posology and method of administration

Posology

Paediatric population

The safety and effectiveness of Sotalol in children under 18 has not been established.

There is no relevant use of Sotalol in the paediatric population.

The initiation of treatment or changes in dosage with sotalol should follow an appropriate medical evaluation including ECG control with measurement of the corrected QT interval, and assessment of renal function, electrolyte balance and concomitant medications (see Section 4.4 Special warnings and special precautions for use).

As with other antiarrhythmic agents, it is recommended that sotalol be initiated and doses increased in a facility capable of monitoring and assessing cardiac rhythm. The dosage must be individualized and based on the patient's response. Proarrhythmic events can occur not only at initiation of therapy, but also with each upward dosage adjustment.

In view of its β -adrenergic blocking properties, treatment with sotalol should not be discontinued suddenly, especially in patients with ischaemic heart disease (angina pectoris, prior acute myocardial infarction) or hypertension, to prevent exacerbation of the disease (see Section 4.4 Special warnings and special precautions for use).

Method of administration

The following dosing schedule can be recommended:

The initial dose is 80 mg, administered either singly or as two divided doses.

Oral dosage of sotalol should be adjusted gradually allowing 2-3 days between dosing increments in order to attain steady-state, and to allow monitoring of QT intervals. Most patients respond to a daily dose of 160 to 320 mg administered in two divided doses at approximately 12 hour intervals. Some patients with life-threatening refractory ventricular arrhythmias may require doses as high as 480 - 640 mg/day. These doses should be used under specialist supervision and should only be prescribed when the potential benefit outweighs the increased risk of adverse events, particularly proarrhythmias (see Section 4.4 Special warnings and special precautions for use).

Dosage in renally impaired patients

Because sotalol is excreted mainly in urine, the dosage should be reduced when the creatinine clearance is less than 60 ml/min according to the following table:

<u>Creatinine clearance (ml/min)</u>	<u>Adjusted doses</u>
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> 60	Recommended sotalol Dose
30-60	½ recommended sotalol Dose
10-30	¼ recommended sotalol Dose
< 10	Avoid

The creatinine clearance can be estimated from serum creatinine by the Cockcroft and Gault formula:

$$\text{Men: } \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}}$$

Women: as above x 0.85

When serum creatinine is given in $\mu\text{mol/l}$, divide the value by 88.4 (1mg/dl = 88.4 $\mu\text{mol/l}$).

Dosage in hepatically impaired patients

Since Sotalol is not subject to firstpass metabolism, patients with hepatic impairment show no alteration in clearance of Sotalol. No dosage adjustment is required in hepatically impaired patients.

4.3 Contraindications

Sotalol should not be used where there is evidence of:

- sick sinus syndrome;
- second and third degree AV heart block (unless a functioning pacemaker is present);
- congenital or acquired long QT syndromes;
- torsades de pointes;
- symptomatic sinus bradycardia;
- uncontrolled congestive heart failure;
- cardiogenic shock;
- anaesthesia that produces myocardial depression;
- untreated phaeochromocytoma;
- hypotension (except due to arrhythmia);
- Raynaud's phenomenon and severe peripheral circulatory disturbances;
- history of chronic obstructive airway disease or bronchial asthma (a warning will appear on the label);
- hypersensitivity to sotalol, other beta-blockers or any of the excipients in the tablet;
- metabolic acidosis;

- renal failure (creatinine clearance < 10 ml/min).

4.4 Special warnings and precautions for use

Abrupt Withdrawal: Hypersensitivity to catecholamines is observed in patients withdrawn from beta-blocker therapy. Occasional cases of exacerbation of angina pectoris, arrhythmias, and in some cases, myocardial infarction have been reported after abrupt discontinuation of therapy. Patients should be carefully monitored when discontinuing chronically administered sotalol, particularly those with ischaemic heart disease. If possible the dosage should be gradually reduced over a period of one to two weeks, if necessary at the same time initiating replacement therapy. Abrupt discontinuation may unmask latent coronary insufficiency. In addition, hypertension may develop.

Proarrhythmias: The most dangerous adverse effect of Class I and Class III antiarrhythmic drugs (such as sotalol) is the aggravation of pre-existing arrhythmias or the provocation of new arrhythmias. Drugs that prolong the QT-interval may cause torsades de pointes, a polymorphic ventricular tachycardia associated with prolongation of the QT-interval. Experience to date indicates that the risk of torsades de pointes is associated with the prolongation of the QT-interval, reduction of the heart rate, reduction in serum potassium and magnesium, high plasma sotalol concentrations and with the concomitant use of sotalol and other medications which have been associated with torsades de pointes (see Section 4.5 Interaction with other medicinal products and other forms of interaction). Females may be at increased risk of developing torsades de pointes. ECG monitoring immediately prior to or following the episodes usually reveals a significantly prolonged QT interval and a significantly prolonged QTc interval. In clinical trials, Sotalol generally has not been initiated to patients whose pretreatment QTc interval exceeded 450 msec. Sotalol should be titrated very cautiously in patients with prolonged QT intervals.

The incidence of torsades de pointes is dose dependent. Torsades de pointes usually occurs early after initiating therapy or escalation of the dose and can progress to ventricular fibrillation.

Clinical studies for arrhythmia: During clinical trials, 4.3% of 3257 patients with arrhythmias experienced a new or worsened ventricular arrhythmia, including sustained ventricular tachycardia (approximately 1%) and torsade de pointes (2.4%). In addition, in approximately 1% of patients, deaths were considered possibly drugrelated. In patients with other, less serious, ventricular arrhythmias and supraventricular arrhythmias, the incidence of torsade de pointes was 1% and 1.4%, respectively.

Serious proarrhythmias including torsade de pointes were dose related as indicated below:

Percent Incidence of Serious Proarrhythmias * by Dose For Patients With

Sustained VT/VF		
Daily Dose (mg)	Incidence of Serious Proarrhythmias*	Patients (n)
1-80	0	(0/72)
81-160	0.5%	(4/838)
161-320	1.8%	(17/960)
321-480	4.5%	(21/471)
481-640	4.6%	(15/327)
>640	6.8%	(7/103)

*Torsade de Pointes or New Sustained VT/VF

In clinical trials of patients with sustained VT/VF the incidence of severe proarrhythmia (torsades de pointes or new sustained VT/VF) was <2% at doses up to 320 mg. The incidence more than doubled at higher doses.

Other risk factors for torsades de pointes were excessive prolongation of the QTc and history of cardiomegaly or congestive heart failure. Patients with sustained ventricular tachycardia and a history of congestive heart failure have the highest risk of serious proarrhythmia (7%).

Proarrhythmic events must be anticipated not only on initiating therapy but with every upward dose adjustment. Initiating therapy at 80 mg with gradual upward dose titration thereafter reduces the risk of proarrhythmia. In patients already receiving sotalol caution should be used if the QTc exceeds 500msec whilst on therapy, and serious consideration should be given to reducing the dose or discontinuing therapy when the QTc-interval exceeds 550 msec. Due to the multiple risk factors associated with torsades de pointes, however, caution should be exercised regardless of the QTc-interval.

Electrolyte Disturbances: Sotalol should not be used in patients with hypokalaemia or hypomagnesaemia prior to correction of imbalance; these conditions can exaggerate the degree of QT prolongation, and increase the potential for torsades de pointes. Special attention should be given to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhoea or patients receiving concomitant magnesium- and/or potassium-depleting drugs.

Congestive Heart Failure: Beta-blockade may further depress myocardial contractility and precipitate more severe heart failure. Caution is advised when initiating therapy in patients with left ventricular dysfunction controlled by therapy (i.e. ACE Inhibitors, diuretics, digitalis, etc); a low initial dose and careful dose titration is appropriate.

Recent MI: In post-infarction patients with impaired left ventricular function, the risk versus benefit of sotalol administration must be considered.

Careful monitoring and dose titration are critical during initiation and followup Of therapy. The adverse results of clinical trials involving antiarrhythmic drugs (i.e. apparent increase in mortality) suggest that Sotacor should be avoided in patients with left ventricular ejection fractions $\leq 40\%$ without serious ventricular arrhythmias. In a large controlled trial in patients with a

recent myocardial infarction without heart failure, who did not necessarily have ventricular arrhythmias, oral sotalol HCl treatment was associated with a nonstatistically significant risk reduction in mortality compared to the placebo group (18%). In this postinfarction study using a fixed dose of 320mg once daily and in a second small randomized trial in high risk postinfarction patients with left ventricular ejection fractions $\leq 40\%$ treated with high doses (640 mg/day), there were suggestions of an excess of early sudden deaths.

Electrocardiographic Changes: Excessive prolongation of the QT-interval, >500 msec, can be a sign of toxicity and should be avoided (see Proarrhythmias above). Sinus bradycardia has been observed very commonly in arrhythmia patients receiving sotalol in clinical trials. Bradycardia increases the risk of torsades de pointes. Sinus pause, sinus arrest and sinus node dysfunction occur in less than 1% of patients. The incidence of 2nd- or 3rd-degree AV block is approximately 1%.

Anaphylaxis: Patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge while taking beta-blockers. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reaction.

Anaesthesia: As with other beta-blocking agents, sotalol should be used with caution in patients undergoing surgery and in association with anaesthetics that cause myocardial depression, such as cyclopropane or trichloroethylene.

Diabetes Mellitus: Sotalol should be used with caution in patients with diabetes (especially labile diabetes) or with a history of episodes of spontaneous hypoglycaemia, since beta-blockade may mask some important signs of the onset of acute hypoglycaemia, e.g. tachycardia.

Thyrotoxicosis: Beta-blockade may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm.

Hepatic Impairment: Since Sotalol is not subject to first-pass metabolism, patients with hepatic impairment show no alteration in clearance of Sotalol.

Renal Impairment: As sotalol is mainly eliminated via the kidneys the dose should be adjusted in patients with renal impairment (see section 4.2).

Psoriasis: Beta-blocking drugs have been reported rarely to exacerbate the symptoms of psoriasis vulgaris.

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

4.5 Interaction with other medicinal products and other forms of interaction

Antiarrhythmics: Class Ia antiarrhythmic drugs, such as disopyramide, quinidine and procainamide and other Class III antiarrhythmic drugs such as amiodarone and bepridil are not recommended as concomitant therapy with sotalol, because of their potential to prolong refractoriness (see Section 4.4 Special warnings and special precautions for use). The concomitant use of other beta-blocking agents with sotalol may result in additive Class II effects.

Other drugs prolonging the QT-interval: Sotalol should be given with extreme caution in conjunction with other drugs known to prolong the QT-interval such as phenothiazines, tricyclic antidepressants, terfenadine and astemizole. Other drugs that have been associated with an increased risk for torsades de pointes include erythromycin IV, halofantrine, pentamidine, and quinolone antibiotics.

Floctafenine: Beta-adrenergic blocking agents may impede the compensatory cardiovascular reactions associated with hypotension or shock that may be induced by Floctafenine.

Calcium channel blocking drugs: Concurrent administration of beta-blocking agents and calcium channel blockers has resulted in hypotension, bradycardia, conduction defects, and cardiac failure. Beta-blockers should be avoided in combination with cardiodepressant calcium-channel blockers such as verapamil and diltiazem because of the additive effects on atrioventricular conduction, and ventricular function.

Potassium-depleting diuretics: Hypokalaemia or hypomagnesaemia may occur, increasing the potential for torsade de pointes (see Section 4.4 Special warnings and special precautions for use).

Other potassium-depleting drugs: Amphotericin B (IV route), corticosteroids (systemic administration), and some laxatives may also be associated with hypokalaemia; potassium levels should be monitored and corrected appropriately during concomitant administration with sotalol.

Clonidine: Beta-blocking drugs may potentiate the rebound hypertension sometimes observed after discontinuation of clonidine; therefore, the beta-blocker should be discontinued slowly several days before the gradual withdrawal of clonidine.

Digitalis glycosides: Single and multiple doses of sotalol do not significantly affect serum digoxin levels. Proarrhythmic events were more common in sotalol treated patients also receiving digitalis glycosides; however, this may be related to the presence of CHF, a known risk factor for proarrhythmia, in patients receiving digitalis glycosides. Association of digitalis glycosides with beta-blockers may increase auriculo-ventricular conduction time.

Catecholamine-depleting agents: Concomitant use of catecholamine-depleting drugs, such as reserpine, guanethidine, or alpha methyl dopa, with a beta-blocker may produce an excessive reduction of resting sympathetic nervous tone. Patients should be closely monitored for evidence of hypotension and/or marked bradycardia which may produce syncope.

Insulin and oral hypoglycaemics: Hyperglycaemia may occur, and the dosage of antidiabetic drugs may require adjustment. Symptoms of hypoglycaemia (tachycardia) may be masked by beta-blocking agents.

Neuromuscular blocking agents like Tubocurarin: The neuromuscular blockade is prolonged by beta-blocking agents.

Beta-2-receptor stimulants: Patients in need of beta-agonists should not normally receive sotalol. However, if concomitant therapy is necessary beta-agonists may have to be administered in increased dosages.

Drug/Laboratory interaction: The presence of sotalol in the urine may result in falsely elevated levels of urinary metanephrine when measured by photometric methods. Patients suspected of having phaeochromocytoma and who are treated with sotalol should have their urine screened utilizing the HPLC assay with solid phase extraction.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Animal studies with sotalol hydrochloride have shown no evidence of teratogenicity or other harmful effects on the foetus. Although there are no adequate and well-controlled studies in pregnant women, sotalol hydrochloride has been shown to cross the placenta and is found in amniotic fluid. Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur in foetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Therefore, sotalol should be used in pregnancy only if the potential benefits outweigh the possible risk to the foetus. The neonate should be monitored very carefully for 48 - 72 hours after delivery if it was not possible to interrupt maternal therapy with sotalol 2-3 days before the birthdate.

Breastfeeding

Most beta-blockers, particularly lipophilic compounds, will pass into breast milk although to a variable extent. Breast feeding is therefore not recommended during administration of these compounds.

4.7 Effects on ability to drive and use machines

There are no data available, but the occasional occurrence of side-effects such as dizziness and fatigue should be taken into account (see Section 4.8 Undesirable effects).

4.8 Undesirable effects

Sotalol is well tolerated in the majority of patients, with the most frequent adverse effects arising from its betablockade properties. Adverse effects are usually transient in nature and rarely necessitate interruption of, or withdrawal from treatment. These include dyspnoea, fatigue, dizziness, headache, fever, excessive bradycardia and/or hypotension. If they do occur, they usually disappear when the dosage is reduced. The most significant adverse effects, however, are those due to proarrhythmia, including torsades de pointes (see section 4.4).

Frequency is defined using the following convention: 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. The following are adverse events considered related to therapy with Sotalol:

System Organ Class	Common	Unknown
Cardiac disorders	Bradycardia Dyspnoea Chest pain Palpitations Oedema Electrocardiogram abnormal Hypotension Arrhythmia Syncope Presyncope Cardiac failure	
Skin and subcutaneous tissue disorder	Rash	Alopecia Hyperhidrosis
Gastrointestinal disorder	Nausea Vomiting Diarrhoea Dyspepsia Abdominal pain Flatulence	
Musculoskeletal, connective tissue and bone disorders	Muscle spasms	
Nervous system disorders	Headache Dizziness Fatigue Asthenia Lightheadedness	

	Paraesthesia Dysgeusia	
Psychiatric disorders	Sleep disorder Mood altered Depression Anxiety	
Reproductive system and breast disorders	Sexual dysfunction	
Eye disorders	Visual disturbance	
Ear and labyrinth disorders	Hearing disturbances	
General disorders and administration site conditions	Pyrexia	
Blood and lymphatic system disorders		Thrombocytopenia

In clinical trials, 3256 patients with cardiac arrhythmias (1363 with sustained ventricular tachycardia) received oral Sotalol, of whom 2451 received the drug for at least two weeks.

The most significant adverse events were torsade de pointes and other serious new ventricular arrhythmias (see section 4.4), which occurred at the following rates:

Patient Populations			
	VT/VF (n=1,363)	NSVT/PVC (n=946)	SVA (n=947)
Torsade de Pointes	4.1%	1.0%	1.4%
Sustained VT/VF	1.2%	0.7%	0.3%

VT = ventricular tachycardia; VF = ventricular fibrillation; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular contraction; SVA = supraventricular arrhythmia.

Overall, discontinuation because of unacceptable adverse events was necessary in 18% of all patients in cardiac arrhythmia trials. The most common adverse events leading to discontinuation of Sotacor are listed in the table below:

-fatigue	4%
-bradycardia(<50 bpm)	3%
-dyspnoea	3%
-proarrhythmia	2%
-asthenia	2%
-dizziness	2%

Cold and cyanotic extremities, Raynaud's phenomenon, increase in existing intermittent claudication and dry eyes have been seen in association with other betablockers.

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 or search for MHRA on Google Play or Apple App store.

4.9 Overdose

Intentional or accidental overdosage with sotalol has rarely resulted in death. Haemodialysis results in a large reduction of plasma levels of sotalol.

Symptoms and treatment of overdosage: The most common signs to be expected are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycaemia. In cases of massive intentional overdosage (2-16 g) of sotalol the following clinical findings were seen: hypotension, bradycardia, prolongation of QT-interval, premature ventricular complexes, ventricular tachycardia, torsades de pointes.

If overdosage occurs, therapy with sotalol should be discontinued and the patient observed closely. In addition, if required, the following therapeutic measures are suggested:

Bradycardia Atropine (0.5 to 2mg IV), another anticholinergic drug, a beta-adrenergic agonist (isoprenaline, 5 microgram per minute, up to 25 microgram, by slow IV injection) or transvenous cardiac pacing.

Heart Block (second and third degree) Transvenous cardiac pacing.

Hypotension Adrenaline rather than isoprenaline or noradrenaline may be useful, depending on associated factors.

Bronchospasm Aminophylline or aerosol beta-2-receptor stimulant.

Torsades de pointes DC cardioversion, transvenous cardiac pacing, adrenaline, and/or magnesium sulphate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, ATC code: C07AA07. D,l-sotalol is a non-selective hydrophilic β -adrenergic receptor blocking agent, devoid of intrinsic sympathomimetic activity or membrane stabilizing activity.

Sotalol has both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) antiarrhythmic properties. Sotalol has no known effect on the upstroke velocity and therefore no effect on the depolarization phase.

Sotalol uniformly prolongs the action potential duration in cardiac tissues by delaying the repolarisation phase. Its major effects are prolongation of the atrial, ventricular and accessory pathway effective refractory periods.

The Class II and III properties may be reflected on the surface electrocardiogram by a lengthening of the PR, QT and QTc (QT corrected for heart rate) intervals with no significant alteration in the QRS duration.

The d- and l-isomers of sotalol have similar Class III antiarrhythmic effects while the l-isomer is responsible for virtually all of the beta-blocking activity. Although significant beta-blockade may occur at oral doses as low as 25 mg, Class III effects are usually seen at daily doses of greater than 160 mg.

Its β -adrenergic blocking activity causes a reduction in heart rate (negative chronotropic effect) and a limited reduction in the force of contraction (negative inotropic effect). These cardiac changes reduce myocardial oxygen consumption and cardiac work. Like other β -blockers, sotalol inhibits renin release. The renin-suppressive effect of sotalol is significant both at rest and during exercise. Like other beta adrenergic blocking agents, sotalol produces a gradual but significant reduction in both systolic and diastolic blood pressures in hypertensive patients. Twenty-four-hour control of blood pressure is maintained both in the supine and upright positions with a single daily dose.

5.2 Pharmacokinetic properties

The bioavailability of oral sotalol is essentially complete (greater than 90%). After oral administration, peak levels are reached in 2.5 to 4 hours, and steady-state plasma levels are attained within 2-3 days. The absorption is reduced by approximately 20% when administered with a standard meal, in comparison to fasting conditions. Over the dosage range 40-640 mg/day sotalol displays dose proportionality with respect to plasma levels. Distribution occurs to a central (plasma) and a peripheral compartment, with an elimination half-life of 10-20 hours. Sotalol does not bind to plasma proteins and is not metabolised. There is very little inter-subject variability in plasma levels. Sotalol crosses the blood brain barrier poorly, with cerebrospinal fluid concentrations only 10% of those in plasma. The primary route of elimination is renal excretion. Approximately 80 to 90% of a dose is excreted unchanged in the urine, while the remainder is excreted in the faeces. Lower doses are necessary in conditions of renal impairment (see Section 4.2 Posology and method of administration). Age does not significantly alter the pharmacokinetics, although impaired renal function in geriatric patients can decrease the excretion rate, resulting in increased drug accumulation.

5.3 Preclinical safety data

No further particulars.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Sodium starch glycollate (Type A)
Magnesium stearate
Hydroxypropyl cellulose
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Blister packs comprising of white opaque PVC filmcoated with PVdC on the inner side with a backing of aluminium foil.

In packs of 7, 14, 21, 28, 56 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirement.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0292

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10 DATE OF REVISION OF THE TEXT

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