

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Difene 100 mg Dual Release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Diclofenac sodium 100mg

Each capsule contains diclofenac sodium 100mg in a modified release formulation (25mg in the form of enteric coated release pellets and 75mg in the form of sustained release pellets)

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Modified release capsule, hard

Size 1, hard gelatin capsules with light blue opaque caps and colourless transparent bodies, printed with "D100M" in white, containing white to cream-coloured spherical pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As a non-steroidal anti-inflammatory analgesic in the symptomatic management of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, acute musculo-skeletal disorders such as peri-arthritis, tendinitis, tenosynovitis, bursitis, sprains, strains and dislocations, relief of pain in fractures, low back pain, acute gout, psoriatic arthropathy. In the management of pain and inflammation associated with orthopaedic, dental and minor surgery.

In the management of dysmenorrhoea and associated menorrhagia.

4.2 Posology and method of administration

For oral use only. Swallow whole, do not chew.

Adults: The usual daily dose is 100 mg in divided doses. This may be increased to 150 mg daily.

Children aged 9 years (min. 35 kg body weight) or over and adolescents should be given up to 2 mg/kg body weight per day in 3 divided doses, depending on the severity of the disorder.

Elderly: NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed. See also Section 4.4, Special warnings and precautions for use.

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4, special warnings and precautions for use).

4.3 Contraindications

- Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1.
- Active gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Cerebrovascular or other active bleeding.
- Last trimester of pregnancy (see 4.6, Fertility, pregnancy and lactation).

- Severe hepatic, renal or cardiac failure (see section 4.4, Special warnings and precautions for use).
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs

4.4 Special warnings and precautions for use

General

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see 4.2, and GI and cardiovascular risks below).

The concomitant use of diclofenac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.

Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug.

Like other NSAIDs, diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac.

Gastrointestinal effects

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs, including diclofenac, and may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the patient should be instructed to consult their doctor and the medicinal product should be withdrawn.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.8). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low-dose acetylsalicylic acid [(ASA)/aspirin] or other medicinal products likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors (see section 4.5, Interaction with other medicinal products and other forms of interaction).

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see 4.8, Undesirable effects).

NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.

Hepatic effects

Close medical surveillance is required when prescribing diclofenac to patients with impaired hepatic function, as their condition may be exacerbated.

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), diclofenac should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

Caution is called for when using diclofenac in patients with hepatic porphyria, since it may trigger an attack.

Renal effects

As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see section 4.3, Contraindications). Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases and in patients receiving long term treatment with diclofenac. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Skin effects

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and generalised bullous fixed drug eruption have been reported very rarely in association with the use of diclofenac (see section 4.8, Undesirable effects). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Diclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cardiovascular and cerebrovascular effects

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy. Clinical trial and epidemiological data suggest that use of diclofenac (particularly at high doses, 150mg daily and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration.

Haematological effects

Use of diclofenac is recommended only for short term treatment. During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Like other NSAIDs, diclofenac may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored

Treatment with diclofenac is associated with several haematopoietic disorders, including thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), pancytopenia, and agranulocytosis. Patients with unexplained haematopoietic disorders may be at increased risk of worsening of their condition and should be monitored.

Pre-existing asthma

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on

NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

Diclofenac should only be given after careful evaluation of the risk/benefit ratio:

– In congenital impairment of porphyrin metabolism (e.g. acute intermittent porphyria);

Other information

Taking NSAIDs at the same time as alcohol can potentiate the undesirable effects caused by the active substance, especially those affecting the gastrointestinal tract.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.

Lithium: If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4).

Other NSAIDs and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section 4.4).

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4).

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

Ciclosporin: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Quinolone antibacterials: There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/cholestyramine.

Potent CYP2C9 inhibitors: "Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfapyrazone and voriconazole), which could result in a significant increase in peak plasma concentration and exposure to diclofenac due to inhibition of diclofenac metabolism.

Aminoglycosides: Reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

Probenecid: Reduction in metabolism and elimination of NSAID and metabolites.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %.

The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. From the 20th week of pregnancy onward, diclofenac use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, diclofenac should not be given unless clearly necessary. If diclofenac is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to diclofenac for several days from gestational week 20 onward. Diclofenac should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligohydramnios (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, diclofenac is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Lactation

Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant.

Fertility

As with other NSAIDs, the use of diclofenac may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac should be considered.

4.7 Effects on ability to drive and use machines

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking diclofenac, should refrain from driving or using machines.

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common: (>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); Not known: cannot be estimated from the available data.

The following undesirable effects include those reported with either short-term or long-term use.

Table 1

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), pancytopenia, agranulocytosis.
Immune system disorders	
Rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension, tachycardia and shock).
Very rare	Angioneurotic oedema (including face oedema).
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common	Headache, dizziness and agitation.
Rare	Somnolence, tiredness
Very rare	Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.
Eye disorders	
Very rare	Visual disturbance, vision blurred, diplopia.
Ear and labyrinth disorders	
Common	Vertigo.
Very rare	Tinnitus, hearing impaired.
Not known	Kounis syndrome.
Cardiac disorders	
Very rare	Palpitations, chest pain, cardiac failure, myocardial infarction.
Vascular disorders	
Very rare	Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare	Asthma (including dyspnoea).
Very rare	Pneumonitis.
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation).

Very rare	Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.
Not known	Ischaemic colitis
Hepatobiliary disorders	
Common	Transaminases increased.
Rare	Hepatitis, jaundice, liver disorder.
Very rare	Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common	Rash.
Rare	Urticaria.
Very rare	Bullous eruptions, exanthema, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura , allergic purpura, pruritus.
Not known	Fixed drug eruption, generalised bullous fixed drug eruption
Renal and urinary disorders	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare	Oedema

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment. (see section 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use).

There have been reports of increased cutaneous and allergic reactions as well as increased NSAID induced hepatotoxicity in patients with systemic lupus erythematosus who are treated with NSAIDs. Aseptic meningitis has also been reported more frequently in NSAID-treated systemic lupus erythematosus patients. Therefore, monitoring is advised when treating these patients with diclofenac.

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 to:

HPRA Pharmacovigilance

Website: www.hpra.ie

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac over dosage. Over dosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic measures

Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g vomiting, gastric lavage) after ingestion of a potentially life threatening overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

M01A B05 Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances, diclofenac.

Diclofenac sodium is a phenylacetic acid derivative and a non-steroidal anti-inflammatory agent with analgesic, anti-inflammatory and anti-pyretic properties. Diclofenac is an inhibitor of cyclo-oxygenase and therefore reduces prostaglandin synthesis. Reduction in prostaglandin levels reduces the inflammatory response by the body.

5.2 Pharmacokinetic properties

The enteric coated pellet component of the preparation ensures quick availability, following rapid gastric passage, of the active component in the blood stream and the sustained release pellet causes a delayed release of the active component.

At therapeutic concentrations, diclofenac is extensively bound (more than 99%) to plasma proteins. It is subject to first pass metabolism and extensively metabolised in the liver (50-60%).

Diclofenac is excreted mostly through the urine with a small amount excreted in the bile, it also enters the synovial fluid and is excreted in breast milk. Diclofenac has a short half-life of about 1-4 hours.

5.3 Preclinical safety data

Animal studies have been carried out in a number of species to determine the toxicity of diclofenac sodium. Acute toxicity studies have been carried out in the rat and when administered orally an LD50 of 53 mg/kg produced behavioural effects and respiratory stimulation. Acute oral toxicity studies in the rabbit showed no toxic effect at a dose of 157 mg/kg.

Toxicity by the intravenous route has been measured in the rat, an administered dose of 117 mg/kg has been shown to have no adverse effect. Intraperitoneal studies have shown a no adverse effect level of 25 mg/kg in the rat, and subcutaneous toxicity in the rat shows a no toxic effect level of 83 mg/kg.

Rectal toxicity has been measured in the rat. An administered dose of 85 mg/kg has been shown to have no adverse effect.

Reproductive toxicity has been studied in both the rat and the rabbit; a dose of 1 mg/kg/day for 21 days in rats has been shown to produce developmental abnormalities of the cardiovascular system. In the rabbit a dose of 10 mg/kg has been shown to reduce fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pellets

Microcrystalline cellulose

Povidone

Methacrylic acid copolymer

Talc

Ammonio methacrylate copolymer type A+B

Colloidal anhydrous silica

Propylene glycol

Sodium hydroxide

Triethyl citrate

Capsule shell

Gelatin

Titanium dioxide E171

Indigo carmine E132

Printing ink

Titanium dioxide E171

Shellac

Propylene Glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister-packs of 28 and 30 capsules.

(Blister strip composed of PVC/PVDC – aluminium).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Glenwood GmbH
Pharmazeutische Erzeugnisse
Arabellastrasse 17
81925 Munich
Germany

8 MARKETING AUTHORISATION NUMBER

PA2256/001/004

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