

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dexametason Abcur 1 mg tablets
Dexametason Abcur 4 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg or 4 mg dexamethasone.

Excipient with known effect:

Each 1 mg tablet contains 73 mg lactose monohydrate.

Each 4 mg tablet contains 70 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

1 mg: Round, biplanar, white to off-white tablets with bevelled edges and single break mark; embossed with „D | 1“, tablet dimension 7 x 2.4 mm.

4 mg: Round, biplane, white to off-white tablets with bevelled edges and single break mark; embossed with „D | 4“, tablet dimension 7 x 2.4 mm.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Conditions in which the anti-inflammatory and immunosuppressive effect of the corticosteroids is desirable. Especially for intensive treatment for a shorter time.
- Cerebral oedema or increased intracranial pressure due to brain tumour
- In the treatment of cancer mammae, ovarii, prostatae or testis when the effect of the corticosteroids is desirable.
- Prophylaxis of emesis induced by emetogenic chemotherapy.
- Diagnostic test of the pituitary and adrenal cortex function
- Dexametason Abcur is indicated in the treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12 years and older with body weight at least 40 kg) who require supplemental oxygen therapy.

4.2 Posology and method of administration

Posology

The dose should be titrated to the individual response and the severity of the disease. To minimize the side effects, the lowest dose that gives effect should be used. The start dose is between 0.5 and 8 mg daily, depending on the disease being treated. More serious medical conditions may require doses of more than 8 mg. The start dose can be retained or adjusted until the patient response is satisfactory.

Conditions in which the anti-inflammatory and immunosuppressive effect of the corticosteroids is desirable: The initial dose is generally 1-4 mg daily for a few days up to a week. In severe acute cases up to 8 mg may be given for a few days. When effect is obtained, the daily dose is gradually decreased by 1-2 mg each third day to a suitable maintenance dose, which is usually 1-2 mg.

Cerebral oedema or increased intracranial pressure due to brain tumour: In the case of cerebral oedema or increased intracranial pressure due to brain tumour, the intravenous administration of glucocorticoids is usually started in severe cases and on improvement a change is made to oral treatment with 4-16 mg Dexametason Abcur daily. In milder cases the oral administration of 2-8 mg is sufficient.

In the treatment of cancer mammae, ovarii, prostatae or testis: The initial dose is generally 8–16 mg. The maintenance dose is 4-12 mg.

Prophylaxis of emesis induced by emetogenic chemotherapy: For the prophylaxis and therapy of cytostatic-induced vomiting, on the day before planned cytostatic therapy 8 mg orally; at the start of therapy 8-12 mg i.v., then 16-24 mg per day orally for a total of 2 days.

Diagnostic test of the pituitary and adrenal cortex function

Inhibition of the pituitary- and adrenal cortex function: 1-4 mg daily. The daily dose should be divided in 2-4 doses throughout the day, and the last is given as late evening dose.

Inhibition test of the pituitary- and adrenal cortex function: Usually a single dose of 2 mg is given at 11-12 pm and a blood sample is withdrawn at 8 am the following morning.

Renal impairment: No dosage adjustment is necessary in patients with impaired renal function (see also section 5.2).

Hepatic impairment: In patients with severe liver disease dose adjustment may be necessary (see also section 5.2).

For the treatment of Covid-19

Adult patients 6 mg PO, once a day for up to 10 days.

Paediatric population

Paediatric patients (adolescents aged 12 years and older) are recommended to take 6mg/dose PO once a day for up to 10 days.

Duration of treatment should be guided by clinical response and individual patient requirements.

Elderly, renal impairment, hepatic impairment

No dose adjustment is needed.

Method of administration

Oral.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Systemic fungal infections

4.4 Special warnings and precautions for use

The patient should be informed that the dose should be increased at fever and stress.

Discontinuation of the dose should be done gradually after long-term treatment. Since the use of corticosteroids suppresses the endogenous secretion of corticotrophin (ACTH) by the anterior pituitary resulting in adrenal cortex atrophy, sudden withdrawal may precipitate acute adrenocortical insufficiency. Therefore, especially after high-dose or prolonged therapy, corticosteroids should only be withdrawn with tapering the dose.

Infections and vaccinations

Extreme caution should be taken at infections and causal treatment should be initiated.

Corticosteroids in high doses may interfere with active immunization. If vaccination with living vaccine has been done shortly before initiation of dexamethasone treatment the administration of dexamethasone should be done under close monitoring. Living vaccine should not be administered during and after dexamethasone therapy.

The use of dexamethasone in active tuberculosis should be restricted to the case of fulminating or disseminated tuberculosis in which corticosteroids are administered in conjunction with a suitable anti-tuberculosis regime. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity close observation is necessary due to the risk of reactivation of the disease. With long-term corticosteroid therapy, these patients should receive prophylaxis with antibiotics.

Treatment of Covid-19

Systemic corticosteroids should not be stopped for patients who are already treated with systemic (oral) corticosteroids for other reasons (e.g. patients with chronic obstructive pulmonary disease) but not requiring supplemental oxygen.

Diabetes

Increased insulin dose for diabetic patients may be necessary at treatment with corticosteroids.

Cerebral edema or increased intracranial pressure

Corticosteroids should not be used in conjunction with a head injury or stroke since they will probably not be of benefit or may even do harm.

Gastrointestinal diseases

Steroids should be used with caution in cases of nonspecific ulcerative colitis if there could be perforation, abscess or other pyogenic infection, diverticulitis, intestinal anastomoses, active or latent peptic ulcer. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving large doses of corticosteroids may be minimal or nonexistent.

Ocular diseases

Prolonged use of corticosteroids may cause posterior subcapsular cataracts, glaucoma with possible damage to the optic nerve and can increase the risk of secondary ocular infections due to fungi or viruses. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

Osteoporosis

Corticosteroids should be used cautiously in patients with osteoporosis as corticosteroids have a negative effect on the calcium balance.

Potassium balance and potassium depleting diuretics

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. It is less likely to occur with synthetic derivatives except when used in large doses. Salt poor diet and potassium supplementation may be necessary. All corticosteroids increase the excretion of calcium.

When corticosteroids administered concomitantly with potassium-depleting diuretics, patients should be observed carefully for the development of hypokalemia.

Myocardial rupture after recent myocardial infarction

According to literature reports, there is an obvious link between the use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction. Treatment with corticosteroids should be used with great caution in these patients.

Salicylates

Caution should be taken at concomitant use of salicylates, especially in patients with hypoprothrombinaemia. If salicylics are given concomitant with a long-term treatment with corticosteroids, a reduction of the corticosteroids should be performed with great caution since otherwise there is a risk of salicylate intoxication.

Patients should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8).

Corticosteroids should be used cautiously in patients with cardiac failure, renal insufficiency, hypertension and migraine, as corticosteroids may cause fluid retention.

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients with haematological malignancies following the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patient at high risk of TLS, such as patients with high proliferative rate, high tumour burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

Paediatric population

Growth and development must be carefully monitored in children since corticosteroids may give rise to early closing of the epiphyses.

Preterm neonates: Available evidence suggests long-term neurodevelopmental adverse events after early treatment (< 96 hours) of premature infants with chronic lung disease at starting doses of 0.25mg/kg twice daily.

Excipient

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

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations with Dexametason Abcur may require dose adjustment;

Phenobarbital, phenytoin, carbamazepine:

Phenobarbital (which is also a metabolite of primidone), phenytoin and carbamazepine alone and in combination induce the metabolism of hydrocortisone, prednisolone, and methylprednisolone (shown in children with asthma) with increased dosage requirements as a result. The interaction is likely for the whole group glucocorticoids. Phenytoin induces the metabolism of dexamethasone and thereby makes the dexamethasone test unreliable. At the same time dexamethasone induces the metabolism of phenytoin with decreased plasma levels as a result.

Itraconazole

Itraconazole decreases the clearance of dexamethasone administered intravenously by 68% by inhibiting CYP 3A4.

Rifampicin

Rifampicin induces the microsomal oxidation of glucocorticoids (hydrocortisone, prednisolone, methylprednisolone). This leads to an increased need of steroids during treatment with rifampicin and a decreased need of steroids after such a treatment.

Primidone

Dexametason Abcur also interacts with primidone which may give rise to a decreased effect of dexamethasone.

Salicylics

Corticosteroids increase the clearance of salicylates which gives a reduction of the plasma clearance. If salicylics are given concomitant with a long-term treatment with corticosteroids the risk of gastrointestinal hemorrhage is increased.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.”

4.6 Fertility, pregnancy and lactation

Pregnancy

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intrauterine growth retardation and effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man. See also section 5.3 of the SmPC. Reduced placenta- and birth weight have been verified after long-term treatment in humans and animals.

Furthermore, there is a risk of adrenal cortex suppression in the newborn child at long-term treatment. A tapered substitution therapy of the newborn may become necessary. Corticosteroids should therefore be given during pregnancy only after specially consideration.

Breast-feeding

Dexamethasone is excreted in human milk to such an extent that effects on the breastfed newborns/infants are likely.

Fertility

Steroids may increase or decrease motility and number of spermatozoa in some patients.

4.7 Effects on ability to drive and use machines

Dexametason Abcur has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

For this medicinal product there is no modern clinical documentation which can act as base for assessment of the frequency of the undesirable effects. Apart from substitution therapy, treatment with corticosteroids always means an overdose in comparison to the physiological condition. Undesired effects of pharmacological doses of corticosteroids are a natural consequence of the pronounced corticoid effect. Unfavorable effects depend on the dose, dosing interval, treatment duration and individual sensitivity.

The undesirable effects are presented within each frequency interval after descending seriousness with the use of the following categories: 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 ($< 1/10\,000$); not known (cannot be estimated from the available data)

System Organ Class	
Infections and infestations	
Common:	Increased susceptibility to infections.
Immune System disorder	
Uncommon:	Hypersensitivity reactions
Endocrine disorders	
Common:	Adrenal suppression, Cushing-like symptoms, growth retardation in children, Diabetes mellitus
Metabolism and nutrition disorders	
Uncommon:	Hypokalemia, sodium retention.
Not known:	Fluid retention, alkalosis hypokalemic
Psychiatric disorders	
Uncommon:	Psychiatric disorders ranging from euphoria, insomnia, mood changes, depression to psychosis.
Nervous system disorders	
Rare:	Intracranial pressure increased.
Not known:	Vertigo, headache
Eye disorders	
Uncommon:	Increased intraocular pressure, glaucoma, posterior cataract, exophthalmia.
Not known:	Chorioretinopathy, vision blurred
Cardiac disorders	
Uncommon:	Cardiac decompensation.
Not known:	Myocardial rupture following recent myocardial infarction
Vascular disorders	
Uncommon:	Thrombosis, hypertension
Not known:	Embolism
Gastrointestinal disorders	
Uncommon:	Gastrointestinal disorders such as nausea, peptic ulcer.
Not known:	Haemorrhagic perforation of the intestine, esophagitis ulcerative, pancreatitis, abdominal distension.
Skin and subcutaneous tissue disorders	
Common:	Acne, hirsutism.
Uncommon:	Skin atrophy, impaired wound healing, suppression of skin tests, skin reactions such as allergic dermatitis, urticaria, angioneurotic edema.
Not known:	Petechiae, erythema, ecchymoses, hyperhidrosis
Musculoskeletal and connective tissue disorders	
Common:	Muscle atrophy, osteoporosis.
Rare:	Aseptic necrosis of bone, tendon rupture.
Not known:	Proximal myopathy, vertebral and longbone fractures, muscle spasm
Reproductive system and breast disorders	
Not known:	Menstrual disorders
General disorders and administration site conditions	
Uncommon:	Oedema, increased appetite
Not known:	Malaise
Investigations	
Common:	Nitrogen balance negative.

Uncommon:	Weight increased
Not known:	Carbohydrate tolerance decreased

The incidence of predictable undesirable effects, including hypothalamic-pituitary adrenal suppression (causing inhibition of ACTH and cortisol), correlates with the duration of treatment, dosage and timing of administration.

Diabetes mellitus may be worsened and latent diabetes become manifest.

The infection defense may be inhibited and thereby the disposition for infection increases. Infections may be activated e.g. tuberculosis.

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 national reporting system listed in [Appendix V*](#).

4.9 Overdose

Toxicity and symptom: Acute toxicity, even with very high doses, does generally not give clinical problems. An acute overdose may possibly aggravate pre-existing disease conditions such as ulcer, electrolyte disturbances, infections and oedema. Most reactions are neuropsychiatric, but seizures and anaphylaxis have been observed. Repeated large doses of methylprednisolone have given liver necrosis and increase of amylase. Bradyarrhythmias, ventricular arrhythmias and cardiac arrest were observed at intravenous administration of large doses of methylprednisolone and dexamethasone.

Treatment: Is not generally required. Gastric lavage and medical coal can be given if needed, moreover symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoid, ATC code: H02AB02

Dexametason Abcur contains dexamethasone, a synthetic corticosteroid with mainly a glucocorticoid effect. The substance has an anti-allergenic, anti-inflammatory and immunosuppressive effect.

The following equivalents facilitate changing to dexamethasone from other glucocorticoids: Milligram for milligram, dexamethasone is approximately equivalent to betamethasone, 4 to 6 times more potent than methylprednisolone and triamcinolone, 6 to 8 times more potent than prednisone and prednisolone, 25 to 30 times more potent than hydrocortisone, and about 35 times more potent than cortisone.

The effect on the electrolyte balance is insignificant with practically no sodium- or fluid retention. The pituitary inhibiting effect is high.

Treatment of COVID-19

The RECOVERY trial (Randomised Evaluation of COVid-19 thERapY,¹) is an investigator-initiated, individually randomised, controlled, open-label, adaptive platform trial to evaluate the effects of potential treatments in patients hospitalised with COVID-19.

¹ www.recoverytrial.net

The trial was conducted at 176 hospital organizations in the United Kingdom.

There were 6425 Patients randomised to receive either dexamethasone (2104 patients) or usual care alone (4321 patients). 89% of the patients had laboratory-confirmed SARS-CoV-2 infection.

At randomization, 16% of patients were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non invasive ventilation), and 24% were receiving neither.

The mean age of patients was 66.1+/-15.7 years. 36% of the patients were female. 24% of patients had a history of diabetes, 27% of heart disease and 21% of chronic lung disease.

Primary endpoint

Mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group, with deaths reported in 482 of 2104 patients (22.9%) and in 1110 of 4321 patients (25.7%), respectively (rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; $P<0.001$).

In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and in those receiving supplementary oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94).

There was no clear effect of dexamethasone among patients who were not receiving any respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

Secondary endpoints

Patients in the dexamethasone group had a shorter duration of hospitalization than those in the usual care group (median, 12 days vs. 13 days) and a greater probability of discharge alive within 28 days (rate ratio, 1.10; 95% CI, 1.03 to 1.17).

In line with the primary endpoint the greatest effect regarding discharge within 28 days was seen among patients who were receiving invasive mechanical ventilation at randomization (rate ratio 1.48; 95% CI 1.16, 1.90), followed by oxygen only (rate ratio, 1.15 ;95% CI 1.06-1.24) with no beneficial effect in patients not receiving oxygen (rate ratio, 0.96 ; 95% CI 0.85-1.08).

Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	<i>no./total no. of patients (%)</i>		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

* Rate ratios have been adjusted for age with respect to the outcomes of 28-day mortality and hospital discharge. Risk ratios have been adjusted for age with respect to the outcome of receipt of invasive mechanical ventilation or death and its subcomponents.

† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.

Safety

There were four serious adverse events (SAEs) related to study treatment: two SAEs of hyperglycaemia, one SAE of steroid-induced psychosis and one SAE of an upper gastrointestinal bleed. All events resolved.

Subgroup analyses

Effects of allocation to DEXAMETHASONE on 28-day mortality, by age and respiratory support received at randomisation²

Effects of allocation to DEXAMETHASONE on 28-day mortality, by respiratory support received at randomisation and history of any chronic disease.³

^{2, 3} (source: Horby P. et al., 2020; <https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1> ; doi: <https://doi.org/10.1101/2020.06.22.20137273>)

5.2 Pharmacokinetic properties

Absorption

Dexamethasone is rapidly and to a large extent absorbed from the gastrointestinal region (80%). The maximum plasma concentration is reached after 1-2 hours.

Distribution

Dexamethasone is bound to plasma proteins to 77%, mainly to albumin. The distribution volume is approx. 0.75 l/kg.

Biotransformation

Dexamethasone is metabolised mainly in the liver but also in the kidney.

Elimination

The plasma elimination half-life of dexamethasone is 3.5-4.5 hours. The half-life for the anti-inflammatory effect is 36-54 hours.

Dexamethasone and its metabolites are excreted in the urine. After oral administration approx. 30% of the total dose is excreted in the urine as unchanged dexamethasone.

Renal and hepatic impairment

In patients with liver disease the clearance for dexamethasone is decreased due to a decreased metabolism in the liver, on the other hand the clearance is increased in patients with kidney failure due to an accelerated metabolism.

5.3 Preclinical safety data

In animal studies, cleft palate was observed in rats, mice, hamsters, rabbits, dogs and primates; not in horses and sheep. In some cases, these divergences were combined with defects of the central nervous system and of the heart. In primates, effects in the brain were seen after exposure. Moreover, intra-uterine growth can be delayed. All these effects were seen at high dosages.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Pack sizes of 20x1, 28x1, 30x1, 50x1, 56x1, 60x1, 98x1 or 100x1 tablets in PVC/PVDC/Alu unit-dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

23 Mar 2021