SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zeqmelit 4 mg orodispersible film
Zeqmelit 6 mg orodispersible film
Zeqmelit 8 mg orodispersible film

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zeqmelit 4 mg orodispersible film
Each orodispersible film contains 4 mg of dexamethasone.

Zeqmelit 6 mg orodispersible film
Each orodispersible film contains 6 mg of dexamethasone.

Zeqmelit 8 mg orodispersible film
Each orodispersible film contains 8 mg of dexamethasone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible film

Zeqmelit 4 mg orodispersible film
White to pale yellow, translucent, rectangular film, 20 mm x 17 mm in dimensions.

Zeqmelit 6 mg orodispersible film
White to pale yellow, translucent, rectangular film, 20 mm x 25 mm in dimensions.

Zeqmelit 8 mg orodispersible film
White to pale yellow, translucent, rectangular film, 20 mm x 33 mm in dimensions.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Processes that require anti-inflammatory and immunosuppressant treatment among others:

- Treatment of cerebral oedema secondary to brain tumours, neurosurgery, brain abscesses
- Treatment of acute severe asthma
- Initial treatment of severe acute dermatological diseases
- Initial treatment of autoimmune diseases
- Treatment of active rheumatoid arthritis
- Prophylaxis and treatment of nausea and vomiting induced by cytostatic agents within the scope of anti-emetic regimens
- Croup
- Allergic reactions, including acute allergic reactions
- 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 required depends on the severity of the disease and the patient's individual response. In general, higher doses are administered initially. The dose tends to be higher during acute severe conditions than during chronic diseases. Once the disease is under control, the patient should be regularly assessed by a physician and the dose should be tapered off to the lowest effective dose (see section 4.4).

When choosing a dose, current treatment guidelines regarding the condition should also be considered.

Adults

Recommended dose:

- Cerebral oedema: a starting dose of 4-8 mg daily is recommended. In emergencies, higher daily doses of 16-24 mg are recommended. During radiotherapy that is given in addition to standard treatment of non-operable brain tumours, low maintenance doses with dexamethasone may be required.

- Acute severe asthma: 16 mg per day for up to two days.

- Severe acute dermatological diseases: 8-40 mg per day depending on the type and duration of the disease, followed by tapering off the doses.

- Autoimmune diseases in the active phase, e.g. systemic erythematous lupus: 6-16 mg per day.

- Rheumatoid arthritis: 4 mg of dexamethasone can be administered when initiating or changing treatment with disease-modifying antirheumatic drugs (DMARDs). In the occurrence of flares, the lowest possible dose should be taken for the shortest duration. Treatment should not exceed three months.

- Prophylaxis and treatment of nausea and vomiting induced by cytostatic agents: single dose of 10-20 mg before commencing chemotherapy. In case of acute emesis: 4-20 mg, depending on the emetic risk of the chemotherapy. In case of delayed emesis: 8 mg, 1 to 2 times per day over a period of 2 to 4 days, depending on the emetic risk of the chemotherapy used.

- Allergic reactions, including acute allergic reactions: 4-10 mg initially, followed by tapering off the doses. Maximum single dose is 12 mg.

- For the treatment of Covid-19: 6 mg once a day for up to 10 days.

Paediatric population

Zeqmelit is only recommended for children above 3 months of age weighing over 7 kg. The maximum single dose is 16 mg.

- Acute severe asthma: 0.6 mg/kg (maximum 16 mg per day) for up to two days.
- Croup: in mild to moderate croup: 0.15-0.6 mg/kg as a single dose, which, if needed, can be repeated once after 24-48 hours. In case of severe croup, 0.6 mg/kg in combination with other treatment options is recommended.
- Allergic reactions, including acute allergic reactions: 0.15-0.6 mg/kg.

Dose / Weight	0,15 mg/kg	0,3 mg/kg	0,6 mg/kg
7 kg	-	-	4 mg
10 kg	-	-	6 mg
13 kg	-	4 mg	8 mg
20 kg	-	6 mg	12 mg
27 kg	4 mg	8 mg	16 mg (maximum dose)
If the strength needed, calculated based on the body weight and dose, is not available, the strength should be rounded up or down to the nearest available strength or to nearest available combination of strengths.			

Treatment of Covid-19
Recommended dose for paediatric patients (adolescents aged 12 years and older) is 6 mg once a day for up to 10 days. Duration of treatment should be guided by clinical response and individual patient requirements.

Hepatic impairment
In patients with severe hepatic impairment dose adjustments may be necessary (see section 5.2).

Renal impairment
No dose adjustment is necessary in patients with renal impairment (see section 5.2).

Method of administration
Zeqmelit orodispersible film should be taken out of each individual sachet in the following way:
- Do not cut the sachet
- Open only at the tear tag
- Tear off slowly
- Check that film is undamaged
- Do not cut or tear the films into smaller pieces
- Use only undamaged films

The mouth should be empty when administering Zeqmelit. Place one film at the time on the tongue with dry fingers. The film rapidly dissolves in the mouth and is then swallowed directly, without water. In case the patient has a dry mouth, a sip of water can be taken prior to the administration of Zeqmelit.

If high doses of dexamethasone (> 48 mg daily) are required, another administration form should be considered, e.g. intravenous administration.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients included in section 6.1.

4.4. Special warnings and precautions for use

Adrenocortical insufficiency
If a long-term treatment with corticosteroids is necessary, the risk of induction of temporary adrenocortical insufficiency should be considered. Because of the long-term action, continued administration may lead to permanent adrenocortical suppression and finally atrophy.

In certain situations of physical stress (e.g. fever attacks, accidents, operations, deliveries), a temporary increase in the daily glucocorticoid dose may be necessary.

Depending on the dose and duration of treatment, the adrenocortical insufficiency induced by glucocorticoids may last for a few months and in individual cases over one year after discontinuing the treatment. Acute adrenocortical insufficiency can be minimised by a gradual, planned reduction of the dose.

Infections and vaccinations

Due to immunosuppression, treatment with dexamethasone may increase the risk of bacterial, viral, fungal or parasitic infections and opportunistic infections. The symptoms of manifest infections or infections in development may be masked, therefore making diagnosis more difficult. Latent infections, including tuberculosis or hepatitis B, may be reactivated.
Special attention should be paid in the following situations:

- Acute and chronic bacterial infections: use specific antibiotic treatment.
- In patients with a history of tuberculosis, only administer dexamethasone together with antituberculosis medicinal products.
- Post-vaccination lymphadenitis with BCG.
- Positive HbsAg chronic hepatitis.
- Acute viral infections, e.g. hepatitis B, herpes zoster varicella, herpes simplex, poliomyelitis, herpetic keratitis, measles.
- Measles or chickenpox: Special protection is recommended in immunosuppressed patients or patients who have not had measles or chickenpox and are in contact with persons with measles or chickenpox. These viral diseases may present an especially severe course in people treated with glucocorticoids.
- Systemic parasitosis and mycosis (e.g. worms, amoeba infection): In patients with significant known or suspected strongyloid infestation, glucocorticoids may lead to activation and dissemination.
- Prophylactic vaccinations with live vaccines (between 8 weeks before and 2 weeks after vaccination). Conversely, it should be considered that administration of inactivated vaccines is, in general, possible. However, the immune reaction and, consequently, the result of vaccination with inactivated vaccines may be compromised when high doses of glucocorticoids are administered.

Pheochromocytoma crisis

Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

Diabetes mellitus difficult to control

Patients with diabetes difficult to control, should be clinically followed up and adjustment of antidiabetic treatment may be necessary.

Osteoporosis

Depending on the duration and dosage of dexamethasone treatment a negative impact on calcium metabolism is expected. Concomitant administration of calcium and, if necessary, vitamin D is recommended. In patients with pre-existing osteoporosis, the need to use additional treatment should be considered. In cases of severe osteoporosis, dexamethasone treatment should only be considered in severe conditions or for short periods of time.

Severe heart failure

Patients with severe heart failure should be carefully monitored.

Difficult to control hypertension

Patients with difficult to control hypertension should receive combined antihypertensive treatment and be monitored at regular intervals.

Psychiatric disorders

Psychiatric disorders, such as hallucinations, emotional instability, irritability, increased activity, and psychosis, may occur in connection with the use of corticosteroids, especially with high doses (see

section 4.8). Typically, symptoms appear after a couple of days or weeks from starting the treatment, but in rare cases symptoms have been reported after a single high dose. Most reactions recover after either dose reduction or treatment withdrawal, although specific treatment may be necessary.
Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders.
Neurological and psychiatric follow-up is recommended.

Intestinal perforation
Due to the risk of intestinal perforation, dexamethasone should only be administered in case of acute indication and under supervision in conditions such as:

- Severe ulcerative colitis with risk of perforation without peritoneal irritation.
- Diverticulitis.
- Enteroanastomosis (immediately after surgery).

Signs of peritoneal irritation subsequent to gastrointestinal perforation may not appear in patients treated with high glucocorticoid doses.

Anaphylactic reactions
Severe anaphylactic reactions may occur (see section 4.8).

Myasthenia gravis
Concomitant myasthenia gravis may initially exacerbate during treatment with dexamethasone.

Hypothyroidism or liver cirrhosis
The effect of corticosteroids is enhanced in patients with hypothyroidism or liver cirrhosis.

Effect on potassium and sodium levels
High doses of dexamethasone require suitable potassium supplements and sodium restrictions in the diet, and plasma potassium levels should be monitored.

Bradycardia
Administration of high doses of dexamethasone may lead to bradycardia.

Tumour lysis syndrome
In the post-marketing experience, tumour lysis syndrome (TLS) has been reported in patients with a malignant haematological process after using dexamethasone alone or in combination with chemotherapeutic agents. Patients with a high risk of TLS such as patients with a high rate of proliferation, high tumour load and high sensitivity to cytotoxic agents should be closely monitored and the appropriate precautions should be taken.

Gastric ulcer
Concomitant treatment with anti-ulcer drugs is recommended.

Closed angle glaucoma, open angle glaucoma, corneal ulcers or lesions
Close ophthalmological monitoring and suitable treatment is recommended.

Visual disturbance
Visual disturbance has been reported with systemic and topical use of corticosteroids. If a patient presents symptoms such as blurred vision or other visual disturbances, it should be considered to refer the patient to an ophthalmologist to evaluate possible causes. These may include cataract, glaucoma, or rare diseases such as central serous chorioretinopathy (CSCR), which has been reported after using systemic and topical corticosteroids.

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.

Treatment duration
Treatment must be limited to the minimum dose for the shortest period.

Long-term treatment
Long term treatment with dexamethasone requires regular medical monitoring (including ophthalmological follow-up every 3 months).

When long-term treatment with glucocorticoids is discontinued, the risk of exacerbation or relapse of underlying disease, adrenocortical insufficiency and cortisone withdrawal syndrome should be considered.

Interference with laboratory tests
Immuno-modulated investigations (e.g. allergy tests): results can be inhibited.

Elderly patients
Elderly patients are in general more sensitive to the risks of dexamethasone treatment, such as osteoporosis. Dexamethasone should therefor only be administered if the risk-benefit ratio of the treatment has been carefully evaluated.

Paediatric population
Use of dexamethasone in the paediatric population must be assessed with focus on the risk-benefit ratio as dexamethasone can delay the growth (see section 4.8).

4.5. Interaction with other medicinal products and other forms of interaction

NSAIDs
The concomitant use of anti-inflammatory or antirheumatic medicinal products (e.g. indomethacin or salicyclates) increases the risk of gastrointestinal ulcer and haemorrhage.

Oral anti-diabetics and insulin
Dexamethasone may reduce the hypoglycaemic effect of oral anti-diabetics and insulin.

CYP3A4-enzyme inducers
CYP3A4-enzyme inducers such as rifampicin, phenytoin, carbamazepine, barbiturates and primidone may reduce the effect of corticosteroids.

CYP3A-inhibitors
It is expected that concomitant treatment with CYP3A-inhibitors, such as ketoconazole and itraconazole, including medicinal products that contain cobicistat, increase the risk of systemic adverse reactions. This combination should be avoided unless the benefit exceeds the increased risk of systemic adverse reactions related to corticosteroids. In this case, patients must be monitored for systemic reactions of corticosteroids.

Ephedrine
Ephedrine may accelerate the glucocorticoid metabolism and thereby reducing the efficacy of glucocorticosteroids.

Coumarin derivatives (oral anticoagulants)
The efficacy of coumarin anticoagulants may be changed (mostly reduced) by concomitant corticosteroid therapy. Concomitant administration may require the anticoagulant dose to be adjusted.

Oestrogens (e.g. for contraceptive use)
Oestrogens may lengthen the half-life of glucocorticoids. Therefore, the clinical effect of glucocorticoids is intensified.

Atropine and other anticholinergic medicinal products
Atropine and other anticholinergic medicinal products may lead to increased intraocular pressure during treatment with dexamethasone.

Cardiac glucosides
The glucoside effect may intensify as a result of potassium deficiency due to treatment with dexamethasone.

Saluretics/laxatives
Concomitant use of saluretics/laxatives with dexamethasone may intensify potassium excretion.

Praziquantel
Glucocorticoids may cause a reduction in blood praziquantel levels.

Chloroquine, hydroxychloroquine, mefloquine
There is an increased risk of myopathy and cardiomyopathy with concomitant use of dexamethasone and chloroquine, hydroxychloroquine or mefloquine.

Immunosuppressant substances
Co-administration of dexamethasone and other immunosuppressant substances increases the susceptibility to infections and potential exacerbation or manifestation of latent infections (e.g. viral, bacterial, fungal, parasitic and opportunistic infections).

Cyclosporine
Co-administration of dexamethasone and cyclosporine may lead to an increase in blood cyclosporine level, which causes a high risk of cerebral convulsions.

Non-depolarising muscular relaxants (rocuronium, vecuronium)
Co-administration of non-depolarising muscular relaxants may prolong muscular relaxation.

Protirelin
Administration of glucocorticoids can reduce the increase in thyroid stimulating hormone (TSH) and this can interfere with the effect of drugs used for diagnostic purposes in thyroid problems.

Fluoroquinolones
The risk of tendon abnormalities may increase when fluoroquinolones are concomitantly used.

Somatropin
The effect of somatropin may be reduced in case of long-term treatment with corticosteroids.

Antacids
Antacids (e.g. magnesium hydroxide and aluminium hydroxide) concomitantly used with dexamethasone can reduce the absorption of glucocorticoids and cause a reduction in the efficacy of dexamethasone. Therefore, these medicinal products should be taken at least 2 hours apart.

4.6. Fertility, pregnancy and lactation

Pregnancy
Dexamethasone crosses the placental barrier. During pregnancy, especially during the first trimester, treatment should only be commenced after evaluating its possible risks and benefits. The half-life of dexamethasone may be prolonged.

Foetal growth abnormalities cannot be ruled out in long-term treatments with corticosteroids during pregnancy. Administration of corticosteroids to pregnant animals may cause abnormalities in foetal development, including cleft palate, inhibited foetal growth and effects on brain growth and development. There is no evidence that corticosteroids lead to increased incidence of congenital abnormalities such as cleft palate/cleft lip in humans. See also section 5.3.

If glucocorticoid treatment occurs at the end of pregnancy, there is a risk of atrophy of the adrenal cortex of the foetus that may require gradually reduced replacement treatment in the infant.

Breastfeeding
Dexamethasone is excreted in breast milk. To date, it is unknown whether dexamethasone leads to harm in breastfed infants. Nonetheless, dexamethasone during the breastfeeding period should only be prescribed when absolutely necessary. It is recommended to stop breastfeeding if the disease requires high doses of dexamethasone.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

The incidences of the Adverse Drug Reactions (ADRs) associated with dexamethasone are listed below. The list is based on adverse events reported during post-marketing use.

The frequency of adverse reactions cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of all below-mentioned adverse events is qualified as "not known".

Depending on dose and duration of treatment, the following adverse reactions may occur according to the MedDRA classification of affected organs and systems:

System organ class	**Not known (cannot be estimated from the available data)**
Blood and lymphatic system disorders	Moderate leucocytosis, lymphopenia, eosinopenia and polycythaemia.
Endocrine disorders	Adrenal insufficiency. Induction of Cushing's syndrome (full moon face, trunk adiposity).
Eye disorders	Glaucoma, cataracts (especially in conjunction with subsequent subcapsular opacity), exacerbation of symptoms of corneal ulcers, fungal, viral and bacterial eye infections, exacerbation of bacterial infections of the cornea, ptosis, mydriasis, chemosis, sclerotic iatrogenic perforation, chorioretinopathy, blurred vision (see also section 4.4).
Gastrointestinal disorders	Peptic ulcer, gastrointestinal haemorrhage, pancreatitis, stomach discomfort.
General disorders and administration site conditions	Delayed scarring of wounds.
Immune system disorders	Hypersensitivity reactions (e.g. exanthema), severe anaphylactic reactions such as arrhythmia, bronchospasm, reduction or increased blood pressure, circulatory failure, cardiac arrest.
Infections and infestations	Masking of infections, manifestation, exacerbation or reactivation of infections (bacterial, viral, fungal, parasitic and opportunistic infections), activation of strongiloidiasis (see section 4.4).

System organ class	Not known (cannot be estimated from the available data)
Metabolism and nutrition disorders	Sodium retention with oedema, increased potassium excretion (that may lead to arrhythmias), increased weight, reduced glucose tolerance, diabetes mellitus, hypercholesterolaemia, hypertriglyceridemia, increased appetite.
Musculoskeletal and connective tissue disorders	Muscular atrophy, muscular weakness, myopathy, tendon abnormalities, tendinitis, tendon ruptures, osteoporosis (dose-dependent, may even occur after short-term treatments), aseptic osteonecrosis, delayed growth in children, epidural lipomatosis, tendon ruptures. Too fast reduction in dose after long-term treatment may cause symptoms such as muscle and joint pains.
Nervous system disorders	Brain pseudotumor (especially in children), manifestations and exacerbation of epilepsy (convulsions).
Psychiatric disorders	Depression, hallucinations, emotional instability, irritability, increased activity, psychosis, mania, euphoria, anxiety, sleep abnormalities, suicidal ideation.
Reproductive system and breast disorders	Abnormal secretion of sex hormones (amenorrhoea, hirsutism, impotence).
Skin and subcutaneous tissue disorders	Steroid acne, red stretch marks, skin atrophy, petechia, telangiectasias, ecchymosis, hypertrichosis, rosaceiform dermatitis (peri-oral), changes to skin pigmentation.
Vascular disorders	Hypertension, increased risk of arteriosclerosis and thrombosis, vasculitis, capillary fragility.

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

No acute intoxication with dexamethasone is known. In case of chronic overdose intensification of reported adverse reactions is expected (see section 4.8), especially those related to the endocrine system, metabolism and electrolytic balance.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids.
Dexamethasone.
ATC code: H02AB02

Dexamethasone is a fluorinated glucocorticoid with very high anti-inflammatory and immunosuppressant actions and weak mineralocorticoid action. Corticosteroids inhibit the synthesis of prostaglandins and leukotrienes, which are substances that mediate vascular and cellular processes of inflammation in addition to the immunological response. This is translated into reduction of vasodilation, reduced fluid exudate, leukocytic activity, aggregation and degranulation of neutrophils, release of hydrolytic lysosomal enzymes, production of superoxide-like free radicals and the number of blood vessels (with less fibrosis) during chronic processes. Both actions correspond to the same mechanism that consist of inhibition of phospholipase A2 synthesis, an enzyme that releases polyunsaturated fatty acids, which are precursors of prostaglandins and leukotrienes.

Dexamethasone has long action duration (biological half-life of 36 hours) and a glucocorticoid effect 7.5 times more potent than that of prednisone or prednisolone, and 30 times more potent than that of hydrocortisone.

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.

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).

Outcome	Dexamethasone (N = 2104)	Usual Care (N = 4321)	Rate or Risk Ratio (95% CI)*
		no./total no. of patients (%)	
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75-0.93)
Secondary outcome			
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.

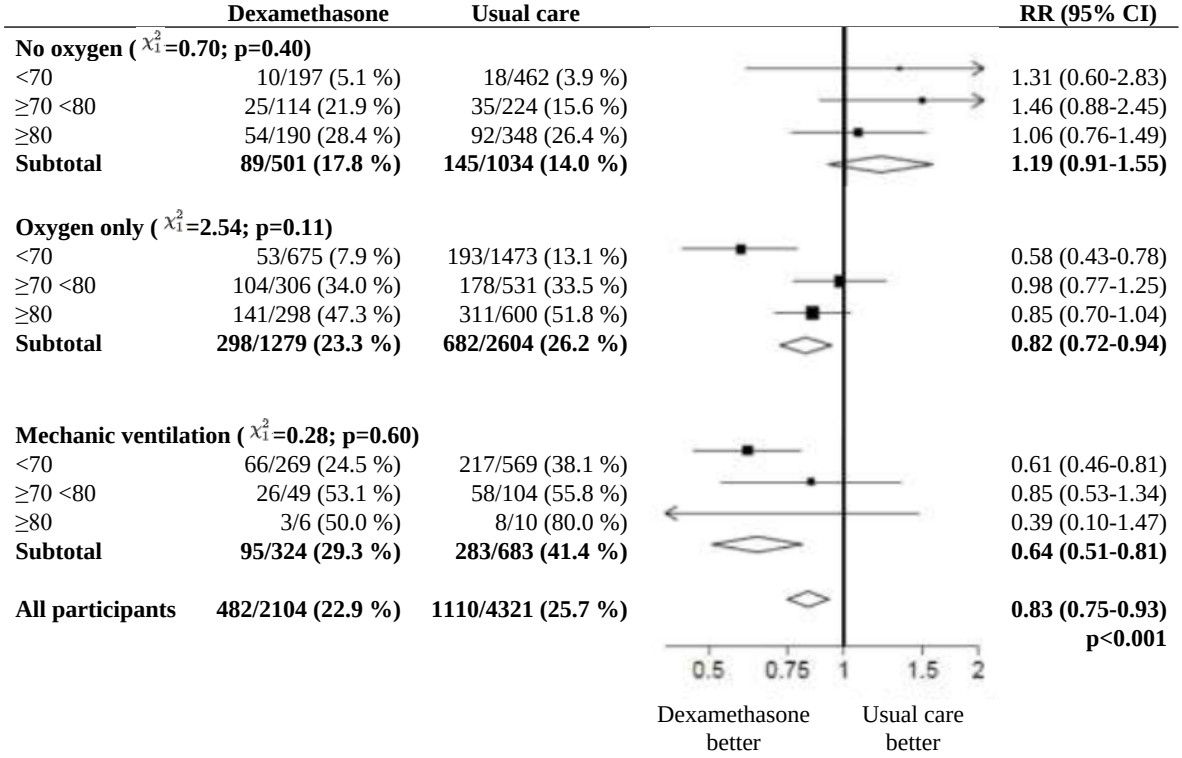
† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.

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

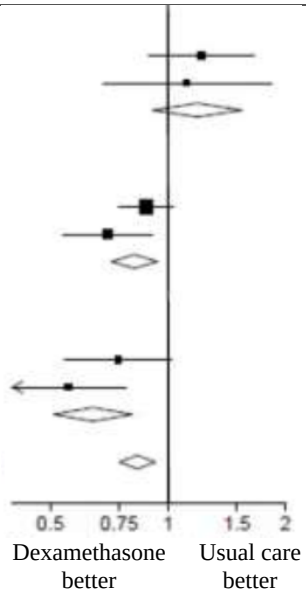
Effects of allocation to DEXAMETHASONE on 28−day mortality, by age and respiratory support received at randomisation



Källa: Horby P. et al., N Engl J Med. 2020 Jul 17

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

	Dexamethasone	Usual care	RR (95% CI)
No oxygen (χ^2_1=0.08; p=0.78)			
Prior disease	65/313 (20.8 %)	100/598 (16.7 %)	1.22 (0.89-1.66)
No prior disease	24/188 (12.8 %)	45/436 (10.3 %)	1.12 (0.68-1.83)
Subtotal	**89/501 (17.8 %)**	**145/1034 (14.0 %)**	**1.19 (0.91-1.55)**
Oxygen only (χ^2_1=2.05; p=0.15)			
Prior disease	221/702 (31.5 %)	481/1473 (32.7 %)	0.88 (0.75-1.03)
No prior disease	77/577 (13.3 %)	201/1131 (17.8 %)	0.70 (0.54-0.91)
Subtotal	**298/1279 (23.3 %)**	**682/2604 (26.2 %)**	**0.82 (0.72-0.94)**
Mechanic ventilation (χ^2_1=1.52; p=0.22)			
Prior disease	51/159 (32.1 %)	150/346 (43.4 %)	0.75 (0.54-1.02)
No prior disease	44/165 (26.7 %)	133/337 (39.5 %)	0.56 (0.40-0.78)
Subtotal	**95/324 (29.3 %)**	**283/683 (41.4 %)**	**0.64 (0.51-0.81)**
All participants	**482/2104 (22.9 %)**	**1110/4321 (25.7 %)**	**0.83 (0.75-0.93)**
			p<0.001



Källa: Horby P. et al., N Engl J Med. 2020 Jul 17

5.2. Pharmacokinetic properties

Absorption
Dexamethasone is absorbed quickly and almost completely in the stomach and small intestine after oral administration. Bioavailability after oral administration is 80% to 90%. Peak plasma concentration is reached 1-2 hours after administration.

Distribution
Dexamethasone binds to plasma albumin in a dose-dependent manner. At high doses, the majority circulates freely in blood plasma, and in cases of hypoalbuminaemia, the proportion of corticoid not bound to proteins increases.

Metabolism and elimination
The half-life of dexamethasone in adults is approximately 3-6 hours.
Dexamethasone elimination is primarily through metabolism. Dexamethasone is primarily metabolised by hydroxylation in the liver by CYP3A, but also in the kidneys by 11-beta-hydroxysteroid-dehydrogenase isoenzymes. Dexamethasone and its metabolites are excreted in urine.

Renal and hepatic impairment
The pharmacokinetics of dexamethasone are not affected by renal impairment. The terminal half-life of dexamethasone has been shown to increase in patients with severe hepatic impairment.

5.3. Preclinical safety data

Acute and chronic toxicity
Glucocorticoids have very low acute toxicity. There are no data on exposure to chronic toxicity in animals.

Mutagenic and teratogenic potential
Results of investigations performed with glucocorticoids have not revealed any clinically relevant genotoxic properties.

Reproductive toxicity
In animal studies cleft palate was observed in rats, mice, hamsters, rabbits, dogs and primates. In some

cases, these findings were combined with central nervous system and heart defects. Moreover, inhibited foetal growth may occur. All these effects were observed at high doses.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hypromellose
Glycerol

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

The orodispersible film is packaged in a sachet. The material is polyethylene-aluminium-polyethylene terephthalate (PE-Al-PET).

Pack size: 2, 3 or 5 sachets
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AcuCort AB
Scheeletorget 1
223 81 Lund
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

<to be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
<To be completed nationally>

10. DATE OF REVISION OF THE TEXT

2026-03-12