WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/documents/75%20SRA%20clarification_February2017_0.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA734 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 3.3 mg dexamethasone (as sodium phosphate) which is equivalent to 4 mg dexamethasone phosphate or 4.3 mg dexamethasone sodium phosphate.

Excipients with known effect:

Each mL of solution contains about 4.44 mg (0.2 mmol) of sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear colourless or yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA734 trade name] is indicated for the management of conditions responsive to parenteral treatment with a potent glucocorticoid, including:

- cerebral oedema and raised intracranial pressure, such as that associated with malignancies, neurosurgical procedures, cerebral abscess or bacterial (including tuberculous) meningitis
- adjunctive management of refractory shock where additional glucocorticoid support is needed
- prophylaxis and treatment of postoperative or chemotherapy-induced nausea and vomiting
- in palliative care for the management of symptoms such as anorexia, dsypnoea, dysphagia, pain and neoplastic spinal cord compression
- as an alternative to other potent glucocorticoids in the acute management of severe corticosteroid-responsive allergic, inflammatory and autoimmune disorders.

[HA734 trade name] is indicated particularly for initial acute management where oral treatment is not feasible.

Local (intra-articular or intralesional) injection of [HA734 trade name] may be given as part of the short-term management of inflammatory joint and tendon disorders, and localised inflammatory and hypertrophic skin lesions including those of lichen simplex, lichen planus, granuloma annulare, discoid lupus erythematosus, and keloids.

[HA734 trade name] may also be used in the treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12 years and older with body weight of at least 40 kg) who require supplemental oxygen therapy.

4.2 Posology and method of administration

Posology

Doses of [HA734 trade name] are calculated in terms of dexamethasone phosphate.
DOSAGE SHOULD BE INDIVIDUALISED BASED ON THE DISEASE AND THE RESPONSE OF THE PATIENT

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Intravenous and intramuscular route

The usual initial dose of dexamethasone phosphate varies between 0.4 and 9 mg a day, depending on the disease being treated. Doses of less than 0.4 mg may be sufficient in less severe conditions while severe and life-threatening diseases may require up to 20 mg or more a day.

The lowest effective dose should be used for the minimum period and this should be reviewed frequently to appropriately titrate the dose against disease activity. If the condition allows it, [HA734 trade name] should be given as a single daily dose (daytime) or a single dose every second day, to reduce suppression of the hypothalamic-pituitary-adrenal (HPA) axis.

The initial dose should be maintained or adjusted until the clinical response is satisfactory and, if no suitable clinical response is obtained after a reasonable period of time, [HA734 trade name] should be stopped and the patient's treatment changed.

Once an initial favourable response has been obtained, the initial dose should be reduced in small amounts until the lowest dose that maintains a suitable clinical response is obtained. The patient should be observed closely for signs that the dose may need to be altered, such as changes in clinical status resulting from disease remissions or exacerbations. It may be necessary to increase the dose temporarily during periods of stress (for example surgery, infection, trauma, etc.).

For the treatment of *cerebral oedema*, [HA734 trade name] may be given intravenously in an initial dose of 8 mg, followed by 4 mg every 6 hours intramuscularly, until the cerebral oedema symptoms have remitted. Response is normally achieved after 12–24 hours and dosage may be reduced after 2 to 4 days and gradually withdrawn over a period of 5 to 7 days. Where cerebral oedema is associated with a brain tumour, palliative maintenance treatment with 2 mg two or three times a day may be effective.

For the treatment of *Covid-19*, [HA734 trade name] is given intravenously in adults at a dose of 6 mg once a day for up to 10 days. Duration of treatment should be guided by clinical response and individual patient requirements. No dose adjustment is needed in the elderly, and in patients with renal or hepatic impairment.

Paediatric population

In children, recommended daily doses have typically ranged from 0.08–0.4 mg/kg.

For the treatment of *Covid-19*, paediatric patients (adolescents aged 12 years and older) are recommended to take 6 mg once a day for up to 10 days.

Withdrawal

If, after several days of treatment, the administration of the drug has to be suspended, it may need to be withdrawn gradually, taking into account the likelihood of suppression of the HPA axis and the risk of disease relapse.

Doses of up to 6 mg daily of dexamethasone for up to 3 weeks are considered unlikely to lead to clinically relevant HPA-axis suppression in the majority of patients (see section 4.4)

Intraarticular and intralesional route and injection into soft tissues

Dosage and frequency of *local administration* vary depending on status and administration site; the usual dose is 0.2 to 6 mg and the frequency may vary from once every 3–5 days to once every 2–3 weeks.

Some recommended doses are as follows:

Injection site	**Dose**
Large joints (knee)	2–4 mg
Small joints (phalangeal, temporo-mandibular)	0.8–1 mg
Bursae	2–3 mg

Tendinous sheaths	0.4–1 mg
Infiltration of soft tissues	2–6 mg
Nodes	1–2 mg

Method of administration.

Intravenous and intramuscular route

[HA734 trade name] may be injected directly or be added to a solution of physiological saline solution or glucose solution and given by intravenous infusion.

Rapid intravenous injection of massive doses of glucocorticoids may sometimes cause cardiovascular collapse; such high-dose injections should therefore be given slowly over a period of several minutes.

Infusion mixtures must be used within 24 hours and the usual aseptic techniques for injections should be observed.

Intraarticular and intralesional route and injection into soft tissues

Local administration should only be used when the affected joints or areas are limited to one or two sites. The repeated administration of intra-articular injections may give rise to articular tissue lesions.

Intra-articular injections should be given under strictly aseptic conditions.

[HA734 trade name] is particularly recommended for combined use with a less soluble and longer-acting corticosteroid in intra-articular injections and injections in soft tissues.

4.3 Contraindications

[HA734 trade name] must not be given to patients with hypersensitivity to any of its ingredients (see section 6.1). Anaphylactoid and hypersensitivity reactions have been reported following the injection of dexamethasone.

Use of [HA734 trade name] is contraindicated in patients with systemic infections, unless controlled with an appropriate anti-infective regimen.

Intra-articular injection is additionally contraindicated in patients with unstable joints and intra-articular or intralesional injections must not be given if there is infection at the injection site.

4.4 Special warnings and precautions for use

Systemic corticosteroids should be used with caution in patients with:

- Osteoporosis
- Hypertension or congestive heart failure
- History of severe affective disorders or corticosteroid-induced psychosis
- Diabetes mellitus or family history of diabetes
- Glaucoma
- Previous corticosteroid-induced myopathy
- Myasthenia gravis
- Liver failure
- Renal insufficiency
- Epilepsy
- Migraine
- Incomplete statural growth
- Cushing's syndrome.

In patients with hypothyroidism or in patients with cirrhosis, corticosteroids present an increased pharmacological effect.

It should be borne in mind that intramuscular administration leads to slower absorption.

Intra-articular injection can also produce systemic and local effects. Frequent intra-articular injection may give rise to articular tissue lesions.

Corticosteroids for other conditions in patients with COVID-19

Patients with COVID-19 who do not require supplemental oxygen and who are already being treated with a systemic (oral) corticosteroid for other reasons (e.g. patients with chronic obstructive pulmonary disease) should continue with their corticosteroid therapy. In patients who are candidates for treatment with [HA734 trade name], and who are already receiving systemic corticosteroid treatment, doses of the latter may need to be reduced.

Gastro-intestinal ulceration

Corticosteroids can exacerbate gastric ulceration and lead to perforation, the symptoms of which may be masked at higher doses by their anti-inflammatory properties. [HA734 trade name] should be used with caution in patients with active or latent peptic ulcer, ulcerative colitis, abscess or other pyogenic infection, diverticulitis, or recent intestinal anastomosis.

Infection

Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The clinical presentation may often be atypical, and serious infections may be masked and may reach an advanced stage before being recognised. Treatment with [HA734 trade name] is contraindicated in patients with systemic infection (see section 4.3) unless the infection is being treated with an appropriate anti-infective regimen. Sensitivity to the anti-infective should be confirmed to ensure that the risk of disseminated infection is minimised.

Patients susceptible to becoming infected with varicella or measles and who are being treated with immunosuppressive doses of corticosteroids should be carefully warned to avoid exposure to these germs. [HA734 trade name] must not be given concomitantly with live vaccines. Care is also needed in patients who may have latent tuberculosis or amoebiasis, as corticosteroids may cause reactivation.

The presence of articular effusion during treatment with corticosteroids requires examination to rule out a septic process. A marked increase in pain accompanied by local swelling, extensive restriction of articular mobility, fever and malaise is suggestive of septic arthritis. If this complication occurs, and the diagnosis of articular infection is confirmed, appropriate antimicrobial treatment should be given.

Withdrawal

In treatment with corticosteroids, the lowest possible dose should always be used until the pathological situation is controlled, to reduce the risk of suppression of the hypothalamic-pituitary-adrenal (HPA) axis leading to adrenocortical insufficiency on withdrawal. Withdrawal may give rise to the appearance of symptoms such as severe fatigue, fever, myalgia, arthralgia, malaise, etc., typical of acute adrenocortical failure. This may even occur in patients without evidence of adrenocortical insufficiency.

Abrupt withdrawal of low- or moderate-dose systemic corticosteroid treatment which has continued *for up to 3 weeks* is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses of up to 6 mg daily of dexamethasone for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression in the majority of patients.

In patients who have received more than physiological doses of systemic corticosteroids (approximately 1 mg dexamethasone) for *more than 3 weeks*, withdrawal should not be abrupt. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic

corticosteroids but there is uncertainty about HPA suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose of 1 mg dexamethasone is reached, dose reduction should be slower to allow the HPA-axis to recover.

In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be *considered even after courses lasting 3 weeks or less:*

- patients who have had repeated courses of systemic corticosteroids, particularly where these were for more than 3 weeks.
- when a short course has been prescribed within one year of cessation of long-term therapy (months or years).
- patients receiving doses of systemic corticosteroid greater than 6 mg daily of dexamethasone (or equivalent).
- patients repeatedly receiving doses in the evening.
- patients with other reasons for adrenocortical insufficiency.

During prolonged therapy any inter-current illness, trauma or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

Children and the elderly

The chronic use of dexamethasone involves the risk of adrenal suppression and retarded growth, hence body growth and development should be evaluated carefully during use in children.

In the elderly, particularly in elderly postmenopausal women, it should be remembered that corticosteroids may inhibit intestinal absorption of calcium and osteoblastic activity, which could exacerbate incipient or existing osteoporosis. They may also increase sodium and water retention and blood pressure.

Athletes

Athletes should be informed that this medicinal product may give a positive result in a doping test.

Excipients

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

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Phenytoin, phenobarbital, carbamazepine, aminoglutethimide, adrenaline and rifampicin may increase the metabolic clearance of corticosteroids, leading to reductions in their blood levels and a reduction in their pharmacological activity, thus requiring an adjustment in the corticosteroid dose. These interactions may interfere with the dexamethasone suppression test, and results obtained in patients receiving these medicines should be interpreted with caution.

False negatives have been reported in the dexamethasone suppression test in patients treated with indomethacin; these results should also be interpreted with caution.

Ephedrine may reduce dexamethasone plasma levels, with possible loss of asthma control.

The half-life of corticosteroids such as dexamethasone may be increased by oestrogens, resulting in increased glucocorticoid effects.

Concomitant treatment with CYP3A inhibitors, including ritonavir and 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 effects.

Dexamethasone itself is reported to be a moderate inducer of CYP3A and P-gp. Induction is dose-dependent and occurs after multiple doses. Co-administration of dexamethasone with other drugs that are metabolized by CYP3A (e.g., indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentrations.

Dexamethasone may reduce plasma levels of albendazole, with a possible inhibition of its effect through the induction of its hepatic metabolism. Combination of corticosteroids with isoniazid may also lead to a reduction in plasma levels of the latter.

Concomitant use of corticosteroids such as dexamethasone with fluroroquinolone antibiotics may increase the risk of tendinopathy.

The incidence of gastro-intestinal ulceration and bleeding is increased in patients receiving concomitant non-steroidal anti-inflammatory drugs and corticosteroids. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication.

Prothrombin time should be checked frequently in patients being given coumarin anticoagulants or indandione derivatives with corticosteroids, since the latter alter anticoagulant response. Studies have variously demonstrated both reduction and increase in anticoagulant effects.

Diuretics are antagonised by corticosteroids and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced. Patients should be monitored regularly in order to avoid the development of hypokalaemia. This is also important in patients receiving cardiac glycosides such as digoxin, as hypokalaemia may increase their toxicity.

Glucocorticoids may increase blood glucose concentrations. It may be necessary to adjust the dosage of oral hypoglycaemics or insulin, or of dexamethasone, when administered jointly.

Dexamethasone is unlikely to have a clinically significant effect on remdesivir as remdesivir has a moderate-high hepatic extraction ratio, and is used for a short duration in the treatment of COVID-19. There may be an increased risk of myopathy or cardiomyopathy if given concomitantly with chloroquine or hydroxychloroquine.

This medicinal product may alter laboratory test results in:

– Blood: increased cholesterol and glucose and reduction of calcium, potassium and thyroid hormones
– Urine: increase in glucose
– Skin tests: tuberculin and patch tests for allergy

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

There are no controlled studies on the use of [HA734 trade name] in pregnant women.

The benefit-risk ratio of treatment should be evaluated for each individual; however, since [HA734 trade name] is indicated for the treatment of serious conditions, the benefits of treatment would normally be expected to outweigh the risk.

Studies performed with corticosteroids in *animals* have shown congenital alterations (microcephalia, hepatomegaly, reduction in adrenal medulla size and thymus), but there is no convincing evidence that systemic corticosteroids increase the incidence of congenital abnormalities, including cleft palate or lip, in newborn children.

Prolonged or repeated administration during pregnancy increases the risk of intra-uterine growth restriction but there is no evidence of intra-uterine growth restriction following short-term treatment.

Children born to mothers who have been treated with corticosteroids during pregnancy should be monitored carefully to detect signs of hypoadrenalism but this usually resolves spontaneously after birth and is rarely clinically important.

Lactation

Corticosteroids are excreted in breast milk and breastfeeding during prolonged treatments with high doses might affect the infant's adrenal function and interfere with growth. Monitoring of the infant is recommended.

4.7 Effects on ability to drive and use machines

[HA734 trade name] is not expected to affect the ability to drive vehicles and use machinery. However, if the patient develops side effects that might affect their ability to do so, such as visual disturbances, they should not drive or operate machines until these have resolved.

4.8 Undesirable effects

In most cases, the undesirable effects of [HA734 trade name] are due to the pharmacological action. The incidence of such predictable undesirable effects, including hypothalamic-pituitary-adrenal suppression, correlates with the dosage, timing of administration and the duration of treatment (see also section 4.4).

[HA734 trade name] is usually given for short-term treatment, which may reduce the likelihood of adverse effects.

Tabulated summary of adverse effects

The adverse reactions observed in patients treated with dexamethasone are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000 including isolated reports), not known (cannot be estimated from the available data).

System organ class	Adverse reactions
Infections and infestations	*Common:* reduction in resistance to infections, oropharyngeal candidiasis. *Uncommon:* local infection at the injection site.
Blood and lymphatic system disorders	*Uncommon:* lymphopenia, eosinopenia.
Immune system disorders	*Uncommon:* allergic reaction at injection site, generalised allergic reaction, anaphylaxis.
Endocrine disorders	*Common:* adrenocortical insufficiency. At high doses: signs of adrenal hyperactivity (Cushing's syndrome) with acneiform eruptions. *Uncommon:* amenorrhea. *Not known:* premature epiphyseal closure, growth suppression.
Metabolism and nutrition disorders	*Common:* hyperglycaemia, polyphagia. *Uncommon:* hypokalaemia, acute pancreatitis. *Not known:* weight gain, impaired carbohydrate tolerance, negative protein and calcium balance, increased appetite, sodium and water retention.
Psychiatric disorders	*Uncommon:* psychotic reactions, affective disorders, behavioural disturbances, sleep disturbances, cognitive dysfunction.
Nervous system disorders	*Uncommon:* intracranial hypertension, neurological alterations; with rapid intravenous injection: convulsive crises.
Eye disorders	*Common:* cataracts. *Not known:* chorioretinopathy, corneal or scleral thinning, visual disturbances, blurred vision.
Cardiac disorders	*Uncommon:* heart failure, irregular heartbeats or palpitations with rapid intravenous injection.

Vascular disorders	*Common:* at high doses, hot flashes. *Uncommon:* thromboembolism, oedema, hypertension, reddening of face and cheeks.
Gastrointestinal disorders	*Common:* at high doses: gastric ulcer. *Not known:* gastrointestinal irritation, intestinal perforation.
Skin and subcutaneous tissue disorders	*Common:* delayed wound healing, local allergic reaction. At high doses: hirsutism, cutaneous hyperpigmentation, scleroderma. *Uncommon:* increased sweating. *Not known:* acne, skin atrophy, bruising, telangiectasia, striae.
Musculoskeletal and connective tissue disorders	*Common:* osteoporosis, bone fragility. With prolonged treatments: muscular atrophy. *Uncommon:* muscle weakness. *Not known:* avascular necrosis, vertebral and long bone fractures, tendon rupture, proximal myopathy.
General disorders and administration site conditions	*Not known:* A transient burning or tingling sensation mainly in the perineal area after intravenous injection of large doses of corticosteroid phosphates. Following intra-articular injection: Charcot-like arthropathy, post-injection flare.

Description of selected adverse effects

Psychiatric disorders

A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood, and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations, and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported.

Reactions may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure, although dose levels do not allow prediction of the onset, type, severity or duration of reactions.

Most reactions resolve after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected.

Psychological effects have been reported infrequently on withdrawal of corticosteroids; the frequency is unknown. Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids.

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. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Acute intoxication or death by overdose are extremely rare. The likely symptoms would be an exaggeration of known corticosteroid-related effects, such as anxiety, depression, mental confusion, psychotic reactions, gastrointestinal bleeding, hyperglycaemia, high blood pressure and oedema.

Symptomatic and supportive treatment should be given as appropriate, including oxygen therapy, maintenance of body temperature, adequate fluid intake and control of electrolytes in serum and urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids for systemic use, Glucocorticoids, ATC code: H02AB02

Dexamethasone is a synthetic fluorinated, long-acting, high-potency, anti-inflammatory and immunosuppressive corticosteroid with low mineralocorticoid activity. It has approximately 7 times the anti-inflammatory potency of prednisolone or prednisone and 30 times that of hydrocortisone: thus, 750 micrograms of dexamethasone is roughly equivalent in its glucocorticoid effects to 5 mg of prednisolone or 20 mg of hydrocortisone.

Glucocorticoids cause profound and varied metabolic effects. They also modify immune response to different stimuli.

Dexamethasone and other glucocorticoids bind to cytoplasmic glucocorticoid receptors, and can modulate gene expression directly, or by an interaction with various transcription factors. This inhibits the synthesis or expression of numerous substances associated with inflammation, including cytokines, chemokines, arachidonic acid metabolites, and adhesion molecules. They may also upregulate the production of some anti-inflammatory mediators.

Other actions

Pharmacological doses of exogenous corticosteroids cause suppression of the hypothalamic-pituitaryadrenal (HPA) axis through a negative feedback mechanism.

Glucocorticoids stimulate protein catabolism and induce the enzymes responsible for the metabolism of the amino acids.

Glucocorticoids cause insulin resistance and play a permissive role for catecholamine-induced glycogenolysis both of which increase blood glucose concentration. In the liver, glucocorticoids increase glycogen storage.

Glucocorticoids increase lipolysis and mobilise the fatty acids of the adipose tissue, leading to an increase in fatty acid plasma concentrations. They also reduce bone formation and increase its resorption.

Use in COVID-19

Results from the RECOVERY trial (Randomised Evaluation of COVid-19 thERapY)[‡], a randomised controlled open-label study in patients hospitalised with COVID-19, showed that dexamethasone therapy is of value in patients with the condition who require supplemental oxygen therapy.

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.

[‡] https://www.recoverytrial.net/

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)**	**RR (95% CI)***
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 respect to the outcomes of 28-day mortality and hospital discharge. Risk ratios have been adjusted for age with respect to the outcome pf 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.

5.2 Pharmacokinetic properties

No bioequivalence study was required due to the pharmaceutical formulation of [HA734 trade name]. Therefore, no pharmacokinetic data are available for this product.

Pharmacokinetics of Dexamethasone phosphate

	Dexamethasone
General	
	Dexamethasone is a long-acting corticosteroid, with effects maintained for up to 72 hours.
Absorption	
Absolute bioavailability	100%

Oral bioavailability	Not applicable
Food effect	Not applicable
Intramuscular injection	Following intramuscular administration as the sodium phosphate, maximum plasma dexamethasone concentrations are reached at about one hour.
Distribution	
Volume of distribution (mean)	1–2 L/kg
Plasma proteinbinding*in vitro*	77%
Tissue distribution	Rapidly distributed into tissue compartments and CSF. Dexamethasone crosses the placenta and is distributed into breast milk.
Metabolism	
	Dexamethasone sodium phosphate is hydrolysed to free dexamethasone on administration, with peak concentrations of dexamethasone reached within 5 minutes of an i.v. dose. Dexamethasone is metabolised in the liver via CYP3A4 to 6-hydroxymetbolites.
Active metabolite(s)	NA
Elimination	
Elimination half life	3-6 h (adults)
Mean systemic clearance (Cl/F)	200–250 mL/min
% of dose excreted in urine	Up to 65% of a dose within 24 h, 8% unchanged
% of dose excreted in faeces	NA; small amounts known to be excreted in bile
Pharmacokinetic linearity	NA
Drug interactions *(in vitro)*	Dexamethasone is a substrate for CYP3A4. Inducers of CYP3A4 may increase the metabolic clearance. Inhibitors of CYP3A4 may decrease the metabolic clearance. Dexamethasone as a moderate inducer may increase the clearance of medicines metabolised by CYP3A.

NA: Information not available

Pharmacokinetics in special populations

Renal impairment
Renal dysfunction does not substantially affect the elimination of dexamethasone.

Hepatic impairment
The elimination half-life is prolonged in severe liver disease.

Paediatric population
The elimination half-life in children aged 8-16 years is about 2.8–7.5 h and in children below the age of 2 years is about 2.3–9.5 h.

5.3 Preclinical safety data

The active substance in this product has been available for many years and its side effects and clinical profile are generally well understood and described in previous sections. Therefore no further data are provided.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Sodium hydroxide (pH adjusting agent)
Disodium edetate
Creatinine
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

In-use: Diluted solution should be used within 24 hours when stored at 30°C.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light. Do not freeze. Avoid excursions above 25°C.

6.5 Nature and contents of container

1 mL of solution is filled in a type 1 hydrolytic, amber glass ampoule with a break ring or break point.

Pack sizes: 5 or 10 ampoules are packed in a carton.

6.6 Instructions for use and handling and disposal

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

7. SUPPLIER

Farmak JSC
63 Kyrylivska St.
Kyiv
Ukraine

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA734

9. DATE OF PREQUALIFICATION

5 November 2020

10. DATE OF REVISION OF THE TEXT

November 2020

References

Corticosteroids for COVID-19, Living guidance, 2 September 2020, WHO
https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1
Accessed November 11, 2020

Recovery Trial, EudraCT 2020-001113-21
https://www.recoverytrial.net/

Accessed November 11, 2020

Dexamethasone in hospitalised patients with COVID-19, Procedure under Article 5(3) of Regulation (EC) No 726/2004, European Medicines Agency, Assessment report https://www.ema.europa.eu/en/documents/other/dexamethasone-covid19-article-53-procedure-assessment-report_en.pdf
Accessed November 11, 2020

Dexamethasone 3.3 mg/ml solution for injection (hameln pharma ltd) SmPC, revised 20 Oct 2020 available on Electronic Medicines Compendium [https://www.medicines.org.uk/emc/product/4659/smpc]

Dexamethasone 3.3 mg/ml Solution for Injection (ampoule) (Hospira UK Ltd) SmPC, revised Jan 2020 available on Electronic Medicines Compendium [https://www.medicines.org.uk/emc/product/570/smpc]

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines