Simplified Development Safety Update Report

Title of study	RECOVERY Trial
Investigational Medicinal Product(s)	Dexamethasone (H02AB02) Prednisolone (H02AB06) Hydrocortisone (H02AB09) Oseltamivir (J05AH02)
☒ I confirm the IMP(s) is/are authorized and the SmPC is used as RSI.	
DSUR Number	1
Period covered	29-Feb-2024 to 01-Mar-2025
Name Sponsor	University of Oxford
Address	Boundary Brook House, Oxford, UK, OX3 9GB
Date of the report	29/4/2025
Relevant study (EU CT number and internal number)	2023-507441-29-00
Note: - This DSUR contains safety information about four investigational medicinal product(s) (IMPs) from an investigator initiated clinical trial. The principal investigator has no access to information from other sponsors conducting trials with the same IMP's. - This Development Safety Update Report contains confidential information - This report includes unblinded adverse event data, if applicable.	

Abbreviations

AxMP	Auxiliary Medicinal Product
CA	Competent Authority
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
IMP	Investigational Medicinal Product
MedDRA	Medical Dictionary for Regulatory Activities
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics

Executive Summary

Introduction

RECOVERY is a multi-national, open-label, randomised controlled trial evaluating treatments for patients admitted to hospital with pneumonia. It is classified as a low-intervention trial in the EU and is currently testing two treatments: dexamethasone (or alternative corticosteroids in pregnant and breastfeeding women) and oseltamivir. All IMPs are licensed for use in the EU, and have been commonly used for decades. The population being studied is patients aged ≥18 hospitalised with pneumonia and a diagnosis of influenza or community-acquired pneumonia (CAP). It is currently open in seven EU countries and four non-EU countries.

Investigational drugs

Three corticosteroids (treatment course 10 days, stopped on discharge if sooner)

- Dexamethasone – 6mg once daily, oral or intravenous
- Prednisolone – 40mg once daily, oral (only if pregnant/breastfeeding)
- Hydrocortisone – 80mg twice daily, intravenous (only if pregnant/breastfeeding)

One neuraminidase inhibitor (treatment course 5 days, or 10 days if immunocompromised)

- Oseltamivir – 75mg twice daily, oral

IMPs are defined by their active substance and are supplied by participating hospital pharmacies, with the formulation being the one used in routine care at the site.

Estimated cumulative exposure of clinical trial subjects

Dexamethasone: 378 subjects
Prednisolone and hydrocortisone: 0 subjects
Oseltamivir: 102 subjects

Summary of overall safety assessment

Based on the information described in this DSUR we do not have new safety concerns for any of the IMPs being evaluated in RECOVERY.

Summary of important risks

Corticosteroids (dexamethasone, prednisolone and hydrocortisone): Immunosuppression, hyperglycaemia, gastrointestinal bleeding, fluid retention, adrenal suppression and psychiatric reactions.
Oseltamivir: Rare life-threatening hypersensitivity reactions and fulminant hepatitis

Actions taken for safety reasons

None

Conclusions

We conclude that the information obtained in this reporting period justifies continuation of this investigator initiated study without any modification.

Table of Contents

1. Introduction

ASR number: 1

Reporting period: 29-Feb-2024 to 01-Mar-2025

RECOVERY is a multi-national, open-label, randomised controlled trial evaluating treatments for patients admitted to hospital with pneumonia. In the EU it is classified as a low-intervention trial and is currently testing two treatments: dexamethasone (or an alternative corticosteroid in pregnant or breastfeeding women) and oseltamivir (a neuraminidase inhibitor). All treatments being tested are licensed for use in hospitalised patients in the EU, and have been commonly used for decades in this population, but they lack robust randomised evidence of benefit for patients with bacterial or influenza pneumonia. The population being studied is adults (aged ≥18 years) admitted to hospital with a pneumonia syndrome and a diagnosis of influenza or community-acquired pneumonia (CAP).

The trial started as a COVID-19 platform trial in the UK in 2020 (hence its full name – the Randomised Evaluation of COVID-19 Therapy), but the final COVID-19 comparisons closed in March 2024. It now open in four non-EU countries (UK, Nepal, Indonesia, and Ghana), seven EU countries (Belgium, France, Italy, Netherlands, Romania, Spain and Sweden) and will soon open in four more countries (Estonia, Portugal, South Africa and Vietnam) and two more non-EU . By late 2025 we expect around 60 EU and 70 non-EU sites to be collaborating in the trial.

This ASR reports on four active substances:

Three corticosteroids (treatment course 10 days, stopped on discharge if sooner)

- Dexamethasone – 6mg once daily, oral or intravenous
- Prednisolone – 40mg once daily, oral[1]
- Hydrocortisone – 80mg twice daily, intravenous[1]

  Corticosteroids modify the body's immune response and have potent anti-inflammatory effects, as well as diverse other metabolic effects.

One neuraminidase inhibitor (treatment for 5 days, or 10 days if immunocompromised)

- Oseltamivir – 75mg twice daily, oral[2]

  Neuraminidase inhibitors are influenza antivirals that inhibit the viral neuraminidase enzyme, preventing release of virus from infected cells.

These IMPs are defined by their active substance and are supplied by participating hospital pharmacies, with the formulation being the one used in routine care at the site. No reference IMPs or auxiliary IMP are used in the trial. All relevant safety data from RECOVERY is reported in this ASR.

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[1] Used in pregnant or breastfeeding women instead of dexamethasone. All regimens have similar glucocorticoid potency.

[2] Adjusted in renal impairment: eGFR 10-29ml/min/1.73m^2: 75mg once daily
eGFR <10ml/min/1.73m^2 or haemodialysis/filtration: 75mg single dose

Suspected Serious Adverse Reactions to a study IMP are reportable according to the RECOVERY protocol. If the investigator does not consider an adverse event to be serious and related to a trial IMP then it is not reportable.

2. Worldwide marketing approval status

Not applicable.

3. Actions taken in the reporting period for safety reasons

We have taken no actions for safety reasons during the reporting period of this DSUR, and have received no requests that place limitations on our study.

4. Changes to reference safety information

There have been no changes to the RSI for any IMPs. Summaries of Product Characteristics are used as reference safety information for all IMPs. The current versions used in RECOVERY are:

Dexamethasone

Dexamethasone 2mg tablets, Aspen Pharma, PL 39699/0056, 14-Aug-2022

Dexamethasone 3.3mg/ml solution for injection, Hameln Pharma, PL 01502/0079, 25-Feb-2022

Prednisolone

Prednisolone 10mg tablets, Accord-UK, PL 00142/0843, 23-Mar-2023

Hydrocortisone

Hydrocortisone 100mg powder for solution for infection/infusion, Panpharma, PL 44124/0020, 31-Mar-2023

Oseltamivir

Tamiflu 75mg hard capsules, Roche, EU/1/02/222/001, 25-Jan-2023

These SmPC versions are provided in Appendix 1. The Undesirable Effects section of all SmPCs used in RECOVERY are reviewed annually for changes of relevance to the trial that would require the SmPC to be updated. This was last performed in June 2024, and no changes were identified.

5. Inventory of clinical trials ongoing and completed during the reporting period

Overview of the ongoing Study

EU CT number	Internal protocol number	Country/ Countries	Study design (including randomisation ratio)	Study population	Start date	Planned enrolment	Subject exposure **
2023-507441-29-00	Core protocol V27.0 EU regional protocol appendix V1.0	Belgium France Ghana Indonesia Italy Nepal Netherlands Romania Spain Sweden UK	Open-label, parallel, randomised, controlled platform trial. The comparisons open in the EU, each with 1:1 randomisation. *Patients with CAP* 1) Dexamethasone vs usual care without corticosteroids *Patients with influenza* 2) Dexamethasone vs usual care without corticosteroids 3) Oseltamivir vs usual care without neuraminidase inhibitor	Patients aged ≥18 years hospitalised with pneumonia 1) Clinical diagnosis of CAP with planned antibiotic treatment without influenza, SARS-CoV-2, active tuberculosis or *Pneumocystis* pneumonia 2) Confirmed influenza A or B plus hypoxia (saturations <92% on air or requiring oxygen), without SARS-CoV-2 coinfection 3) Patients with confirmed influenza A or B	UK start dates 1) 17-Jan-2024 2) 29-Dec-2023 3) 13-Oct-2023 EU start date 1-3) 29-Feb-2024	6,000 per comparison	1) 481 randomised 231 allocated dexamethasone 2) 272 randomised 147 allocated dexamethasone 3) 201 randomised 102 allocated oseltamivir
**Based upon total number of patients recruited as of 01-Mar-2025							

6. Estimated cumulative exposure

6.1. Cumulative subject exposure in the study

Treatment	Number of subjects
Dexamethasone	378
Prednisolone	0
Hydrocortisone	0
Oseltamivir	102

6.2. Patient exposure from marketing experience

Not applicable. The study drug is not marketed by the sponsor.

7. Data in line listings and summary tabulations

7.1. Reference information

The Medical Dictionary for Regulatory Activities (MedDRA) version 28.0 is used for the coding of adverse events. The SmPCs listed above serve as reference document for determination of "expectedness" for all adverse events.

7.2. Line listings of serious adverse reactions during the reporting period

Case ID/ Subject number*	Country Gender Age	Serious adverse drug reactions (SARs)	Expected/ unexpected	Date of onset** Time to onset**	Outcome	Suspect Drug	Daily dose Route Formulation	Dates of treatment Treatment duration	Comments
[redacted]	Italy Female 63	Hyperglycemia	Expected	28-Jan-2025 1 day	Resolved, discharged alive	Dexamethasone	6mg daily Intravenous solution for injection	28-Jan-2025 to 29-Jan-2025	Known diabetes mellitus
	Nepal Female 50	Hyperglycemia	Expected	07-Feb-2025 1 day	Resolved, discharged alive	Dexamethasone	6mg daily Intravenous solution for injection	06-Feb-2025 to 08-Feb-2025	No known diabetes mellitus

*Study/Center/subject
**Primary SAR only

7.3. Cumulative summary tabulations of serious adverse events

The table below presents the number of SAEs that have been reported during this clinical trial organized by system organ class.

System organ Class	Metabolism and nutrition disorders	
Preferred term	Dexamethasone	Control
Hyperglycaemia	2	NA*

*As RECOVERY is open label, serious adverse reactions cannot be reported for patients allocated to the control group

8. Significant findings from clinical trials during the reporting period

8.1. Completed clinical trials

Not applicable.

8.2. Ongoing clinical trials

The investigators remain blinded to the results of the ongoing comparisons. The trial Data Monitoring Committee reviewed unblinded data and adverse event reports for all trial comparisons on 22-Mar-2024 and 02-Oct-2024, and did not report emerging safety concerns.

8.3. Long-term follow-up

Not applicable.

8.4. Other therapeutic use of investigational drug

Not applicable.

8.5. New safety data related to combination therapies

Not applicable.

9. Safety findings from non-interventional studies

Not applicable.

10. Other clinical trial/study safety information

Not applicable.

11. Safety findings from marketing experience

None.

12. Non-clinical data

Not applicable.

13. Literature

A review of the scientific, peer-reviewed literature was conducted during for the duration of the current reporting period. In the searches performed no new relevant safety findings for the trial IMPs were reported in published scientific literature.

Dexamethasone, prednisolone and hydrocortisone

One literature review was identified on the safety of steroids for CAP (https://pubmed.ncbi.nlm.nih.gov/39778921/). This did not identify any new relevant safety findings, and concluded "*Corticosteroids are generally safe for acute use in the treatment of severe CAP; the analysed trials and meta-analysis suggest that they are not associated with a*

higher incidence of adverse effects such as HAI [healthcare-associated infection], GI [gastrointestinal] tract bleeding and AKI [acute kidney injury]. They probably increase the risk of hyperglycaemia, but close monitoring of glucose levels and appropriate management strategies should help mitigate this risk."

Oseltamivir

One high-quality meta-analysis of randomised trials of antivirals for severe influenza was published during the reporting period, which looked at efficacy and safety outcomes (https://pubmed.ncbi.nlm.nih.gov/39181595/). The study identified eight trials with 1424 participants, including 699 in trials evaluating oseltamivir. It did not report any new safety concerns for oseltamivir. The study authors concluded that "*The effects of all antivirals on mortality and other important patient outcomes are very uncertain due to scarce data from randomised controlled trials*", and also that "*Additional clinical trials of antivirals are needed to inform the clinical benefit, safety, and effects on antiviral resistance in patients with severe influenza."*

Several publications reported data from the US FDA Adverse Event Reporting System (FAERS), which collects spontaneous post-marketing reports from patients receiving oseltamivir. Many different categories of adverse event were reported in patient receiving oseltamivir, but the reporting biases inherent in this study design and lack of comparable untreated controls mean that they do not provide robust evidence of any new safety concerns. (https://pubmed.ncbi.nlm.nih.gov/38656741/, https://pubmed.ncbi.nlm.nih.gov/39536015/, https://pubmed.ncbi.nlm.nih.gov/38724914/)

14. Other DSURs

Not applicable.

15. Lack of efficacy

Not applicable

16. Region-specific information

[redacted]

17. Late-breaking information

On 22-Apr-2025 the REMAP-CAP platform trial reported their results from an evaluation of hydrocortisone for patients hospitalised with severe CAP. This compared 7 days of hydrocortisone 50mg every 6 hours with control (no corticosteroid). The comparison was stopped for futility after recruitment of 658 patients. Day 90 mortality was 15% (78/521) in the hydrocortisone arm versus 10% (12/122) in the control arm. They concluded that hydrocortisone appears unlikely to yield a large reduction in mortality, but smaller benefits and possible harm are not excluded.

https://link.springer.com/article/10.1007/s00134-025-07861-w

This trial contrasts with previous trials in severe CAP that have suggested a benefit of corticosteroids, for example the CAPE COD trial reported in 2023 (https://www.nejm.org/doi/full/10.1056/NEJMoa2215145). The differing results from these and other previous trials support the need for more randomised evidence to guide the use of corticosteroids in patients hospitalised with CAP.

18. Overall safety assessment

Based on the information described in this DSUR we do not have new safety concerns for any of the IMPs being evaluated in RECOVERY.

18.1. Evaluation of the risks

Not applicable

18.2. Benefit-risk considerations

Not update to the current structured risk analysis in the EU regional appendix.

19. Summary of important risks

Corticosteroids (dexamethasone, prednisolone and hydrocortisone)

The adverse effect profile of corticosteroids is well known and includes several potentially serious reactions, as described in the SmPC. These include immunosuppression with increased risk of secondary infections, hyperglycaemia, peptic ulceration, fluid retention, adrenal

suppression and psychiatric reactions. Common non-serious side effects include nausea, insomnia, and appetite suppression

Oseltamivir

Common side effects such as headache, nausea and vomiting. Oseltamivir is rarely associated with life-threatening adverse reactions, including anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis and fulminant hepatitis, which have been reported in <1 in 1000 patients.

20. Conclusions

We conclude that the information obtained in this reporting period justifies continuation of this investigator initiated study without any modification.

Appendix 1 – SmPC for Dexamethasone 2mg tablets

Dexamethasone 2mg Tablets

Summary of Product Characteristics Updated 14-Aug-2022 | Aspen

1. Name of the medicinal product

Dexamethasone Tablets BP 2.0mg

2. Qualitative and quantitative composition

Each tablet contains 2.0mg dexamethasone PhEur.

Excipient with known effect

Each tablet contains approximately 116mg lactose monohydrate Ph.Eur.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet

White, round and flat tablets with bevelled edges and a diameter of 6 mm, coded XC above, and 8 below on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Indicated in a wide variety of disorders amenable to glucocorticoid therapy, as well as an adjunct in the control of

cerebral oedema.

Dexamthasone 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

In general, glucocorticoid dosage depends on the severity of the condition and response of the patient. Under certain circumstances, for instance in stress and changed clinical picture, extra dosage adjustments may be necessary. If no favourable response is noted within a couple of days, glucocorticoid therapy should be discontinued.

Adults

Usually, daily oral dosages of 0.5 - 10 mg are sufficient. In some patients higher dosages may be temporarily required to control the disease. Once the disease is under control the dosage should be reduced or tapered off to the lowest suitable level under continuous monitoring and observation of the patient. **(See Section 4.4)**

For a short dexamethasone suppression test, 1mg dexamethasone is given at 11 p.m. and plasma cortisol measured the next morning. Patients who do not show a decrease in cortisol can be exposed to a longer test: 500 micrograms dexamethasone is given at 6 hourly intervals for 48 hours followed by 2mg every 6 hours for a further 48 hours. 24 hour-urine collections are made before, during and at the end of the test for determination of 17-hydroxycorticosteroids.

Paediatric population

0.01-0.1mg/kg of body weight daily.

Dosage of glucocorticoids should be adjusted on the basis of the individual patient's response.

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 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.

4.3 Contraindications

Systemic infection unless specific anti-infective therapy is employed.

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

Avoid live vaccines in patients receiving immunosuppressive doses (serum antibody response diminished).

In general no contraindications apply in conditions where the use of glucocorticoids may be lifesaving.

4.4 Special warnings and precautions for use

A patient information leaflet should be supplied with this product.

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. Patients 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.

Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5 for pharmacokinetic interactions that can increase the risk of side effects), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover 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. Patients/carers should also be alert to possible psychiatric

disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

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.

The results of a randomised, placebo-controlled study suggest an increase in mortality if methylprednisolone therapy starts more than two weeks after the onset of Acute Respiratory Distress Syndrome (ARDS). Therefore, treatment of ARDS with corticosteroids should be initiated within the first two weeks of onset of ARDS (see also section 4.2.).

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 0.25 mg/kg twice daily.

Undesirable effects may be minimised by using the lowest effective dose for the minimum period, and by administering the daily requirement as a single morning dose or whenever possible as a single morning dose on alternative days. Frequent patient review is required to appropriately titrate the dose against disease activity.

Dexamethasone withdrawal

Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute adrenal insufficiency, being tapered off over weeks or months according to the dose and duration of treatment.

In patients who have received more than physiological doses of systemic corticosteroids (approximately 1mg dexamethasone) for greater than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. 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 1mg dexamethasone is reached, dose reduction should be slower to allow the HPA-axis to recover.

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

• When a short course has been prescribed within one year of cessation of long-term therapy (months or years).

• Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.

• Patients receiving doses of systemic corticosteroid greater than 6mg daily of dexamethasone.

• Patients repeatedly taking doses in the evening.

During prolonged therapy any intercurrent 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.

Patients should carry 'Steroid treatment' cards which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and the duration of treatment.

Anti-inflammatory/Immunosuppressive effects and 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 such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised.

Appropriate anti-microbial therapy should accompany glucocorticoid therapy when necessary e.g. in tuberculosis and viral and fungal infections of the eye.

Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive

immunisation with varicella zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

Measles. **Patients should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs; prophylaxis with intramuscular normal immunoglobulin may be needed.**

Visual disturbance

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

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

Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary

a. Osteoporosis (post-menopausal females are particularly at risk)

b. Hypertension or congestive heart failure

c. Existing or previous history of severe affective disorders (especially previous steroid psychosis)

d. Diabetes mellitus (or a family history of diabetes)

e. History of tuberculosis

f. Glaucoma (or a family history of glaucoma)

g. Previous corticosteroid-induced myopathy

h. Liver failure

i. Renal insufficiency

j. Hypothyroidism

k. Epilepsy

l. Peptic ulceration

m. Migraine

n. Certain parasitic infestations in particular amoebiasis

o. Incomplete natural growth since glucocorticoids on prolonged administration may accelerate epiphyseal closure

Caution should be exercised when using corticosteroids in patients who have recently suffered myocardial infarction as myocardial rupture has been reported.

After administration of glucocorticoids serious anaphylactoid reactions such as glottis oedema, urticaria and bronchospasm have occasionally occurred particularly in patients with a history of allergy.

If such an anaphylactoid reaction occurs, the following measures are recommended: immediate slow intravenous injection of 0.1-0.5ml of adrenaline (solution of 1:1000: 0.1-0.5mg adrenaline dependent on body weight), intravenous administration of aminophylline and artificial respiration if necessary.

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

Paediatric population

Corticosteroids cause dose-related growth retardation in infancy, childhood and adolescence, which may be irreversible.

Use in the Elderly

The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Rifampicin, rifabutin, carbamazepine, phenobartital, phenytoin, primidone, and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced.

Dexamethasone is a moderate inducer of CYP 3A4. Co-administration of dexamethasone with other drugs that are metabolized by CYP 3A4 (e.g., indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentrations.

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.

Ephedrine also accelerates the metabolism of dexamethasone.

The effects of anticholinesterases are antagonised by corticosteroids in myasthenia gravis.

The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by corticosteroids, and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.

The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

Oral contraceptives (oestrogens and progestogens) increase plasma concentration of corticosteroids. The antiviral drug ritonavir also increases the plasma concentration of dexamethasone.

Dexamethasone reduces the plasma concentration of the antiviral drugs indinavir and saquinavir.

The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication.

Patients taking NSAIDs should be monitored since the incidence and/or severity of gastro-intestinal ulceration may increase.

Patients taking methotrexate and dexamethasone have an increased risk of haematological toxicity.

Antacids, especially those containing magnesium trisilicate have been reported to impair the gastrointestinal absorption of glucocorticoid steroids. Therefore, doses of one agent should be spaced as far as possible from the other.

4.6 Fertility, pregnancy and lactation

Pregnancy

The ability of corticosteroids to cross the placenta varies between individual drugs, however, dexamethasone readily crosses the placenta.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine 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). However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

Breast-feeding

Corticosteroids may pass into breast milk, although no data are available for dexamethasone. Infants of mothers taking high doses of systemic corticosteroids for prolonged periods may have a degree of adrenal suppression.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The incidence of predictable undesirable effects, including hypothalamic-pituitary-adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see section 4.4).

Endocrine/metabolic

Suppression of the hypothalamic-pituitary-adrenal axis, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea, Cushiongoid faces, hirsutism, weight gain, premature epiphyseal closure, impaired carbohydrate tolerance with increased requirement for anti-diabetic therapy, negative protein and calcium balance, increased appetite

Anti-inflammatory and Immunosuppressive effects

Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (see section 4.4), decreased responsiveness to vaccination and skin tests

Musculoskeletal

Osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, proximal myopathy

Fluid and electrolyte disturbance

Sodium and water retention, hypertension, potassium loss, hypokalaemic alkalosis

Neuropsychiatric

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 are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown.

Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal. Aggravation of epilepsy. Psychological dependence.

Ophthalmic

Increased intra-ocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning, exacerbation of opthalmic viral or fungal diseases, chorioretinopathy

Eye disorders

Vision, blurred (see also section 4.4)

Gastrointestinal

Dyspepsia, peptic ulceration with perforation and haemorrhage, acute pancreatitis, oesophagael ulceration and candidiasis, abdominal distension and vomiting

Dermatological

Impaired healing, skin atrophy, bruising, telangiectasia, striae, acne

General

Hypersensitivity, including anaphylaxis and angioedema, have been reported. Leucocytosis, thromboembolism, myocardial rupture following recent myocardial infarction, nausea, malaise, hiccups

Withdrawal symptoms and signs

Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see section 4.4).

A 'withdrawal syndrome' may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

It is difficult to define an excessive dose of a corticosteroid as the therapeutic dose will vary according to indication and patient requirements. Exaggeration of corticosteroid related adverse effects may occur. Treatment should be asymptomatic and supportive as necessary.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Dexamethasone is a synthetic glucocorticoid whose anti-inflammatory potency is 7 times greater than prednisolone. Like other glucocorticoids, dexamethasone also has anti-allergic, antipyretic and immunosuppressive properties.

Dexamethasone has practically no water and salt-retaining properties, and is therefore particularly suitable for use in patients with cardiac failure or hypertension. Because of its long biological half-life (36-54 hours), dexamethasone is especially suitable in conditions where continuous glucocorticoid action is desired.

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 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.

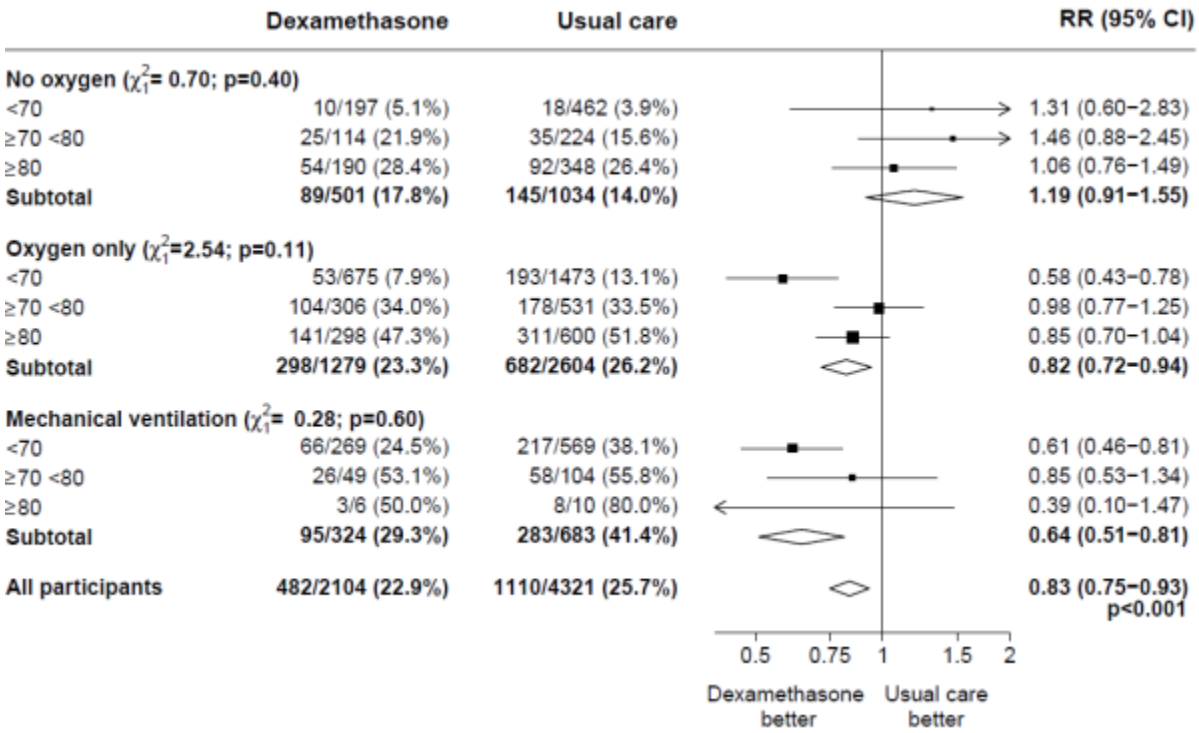
[1] www.recoverytrial.net

Safety

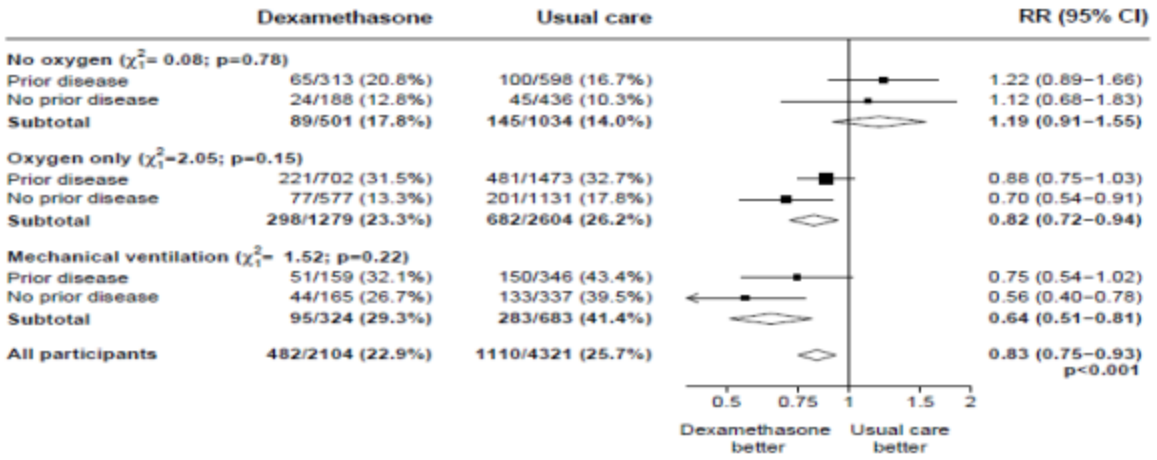
There were four serious adverse events (SAEs) related to study treatment: two SAEs of hyperglycaemia, one SAE of steroid-induced psychosis and one SAE of an upper gastrointestinal bleed. All events resolved.

Subgroup analyses

Effects of allocation to DEXAMETHASONE on 28−day mortality, by age and respiratory support received at randomisation[2]



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

Corticosteroids, are, in general, readily absorbed from the gastro-intestinal tract. They are also well absorbed from sites of local application. Water-soluble forms of corticosteroids are given by intravenous injection for a rapid response; more prolonged effects are achieved using lipid-soluble forms of corticosteroids by intramuscular injection.

Distribution

Corticosteroids are rapidly distributed to all body tissues. They cross the placenta and may be excreted in small amounts in breast milk.

Most corticosteroids in the circulation are extensively bound to plasma proteins, mainly to globulin and less so to albumin. The corticosteroid-binding globulin has high affinity but low binding capacity, while the albumin has low affinity but large binding capacity. The synthetic corticosteroids are less extensively protein bound than hydrocortisone (cortisol). They also tend to have longer half-lives.

Biotransformation and Elimination

Corticosteroids are metabolised mainly in the liver but also in the kidney, and are excreted in the urine. The slower metabolism of the synthetic corticosteroids with their lower protein-binding affinity may account for their increased potency compared with the natural corticosteroids.

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

Potato starch PhEur, propylene glycol PhEur, magnesium stearate PhEur, and lactose PhEur.

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C protected from light.

6.5 Nature and contents of container

White, cylindrical wide mouth containers with screw caps made of high density polyethylene (HDPE) with a child resistant polypropylene screw cap, containing 50, 100 or 500 tablets. Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Aspen Pharma Trading Limited,

3016 Lake Drive,

Citywest Business Campus,

Dublin 24,

Ireland

8. Marketing authorisation number(s)

PL 39699/0056

9. Date of first authorisation/renewal of the authorisation

29/03/1990 / 17/06/2010

10. Date of revision of the text

February 2022

Company Contact Details

Aspen

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Appendix 2 – SmPC for Dexamethasone 3.3mg/ml solution for injection

Dexamethasone 3.3 mg/ml solution for injection

Summary of Product Characteristics Updated 25-Feb-2022 | hameln pharma ltd

1. Name of the medicinal product

Dexamethasone 3.3 mg/ml solution for injection

2. Qualitative and quantitative composition

3.32 mg of dexamethasone (dexamethasone base) in 1 ml solution for injection

6.64 mg of dexamethasone (dexamethasone base) in 2 ml solution for injection

Each ml of solution for injection contains 4.00 mg of dexamethasone phosphate (as 4.37 mg dexamethasone sodium phosphate) equivalent to 3.32 mg of dexamethasone base.

Excipients with known effect

Each ml contains 20 mg of propylene glycol – see section 4.4.

Each ml contains a maximum of 0.42 mg of sodium – see section 4.4.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection

Clear and colourless solution

4. Clinical particulars

4.1 Therapeutic indications

Corticosteroid

For use in certain endocrine and non-endocrine disorders responsive to corticosteroid therapy

Intravenous or Intramuscular administration

Dexamethasone 3.3 mg/ml solution for injection is recommended for systemic administration by intravenous or intramuscular injection when oral therapy is not feasible or desirable in the following conditions.

Endocrine disorders

Primary or secondary adrenocortical insufficiency

(Hydrocortisone or cortisone is the first choice, but synthetic analogues may be used with mineralocorticoids where applicable and, in infancy, mineralocorticoid supplementation is particularly important)

Non-endocrine disorders

Dexamethasone 3.3 mg/ml solution for injection may be used in the treatment of non-endocrine corticosteroid-responsive conditions, including:

Allergy and anaphylaxis

Angioneurotic oedema and anaphylaxis

Coronavirus disease 2019 (COVID-19)

Dexamethasone 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.

Gastrointestinal

Crohn's disease and ulcerative colitis

Infection (with appropriate chemotherapy)

Miliary tuberculosis and endotoxic shock

Neurological disorders

Raised intracranial pressure secondary to cerebral tumours and infantile spasms

Respiratory

Bronchial asthma and aspiration pneumonitis

Skin disorders

Toxic epidermal necrolysis

Shock

Adjunctive treatment where high pharmacological doses are needed. Treatment is an adjunct to and not a substitute for, specific and supportive measures the patient may require. Dexamethasone has been shown to be beneficial when used in the early treatment of shock, but it may not influence overall survival.

Subcutaneous administration

In palliative care, patients receiving corticosteroids for symptoms such as fatigue, anorexia, refractory nausea and vomiting or adjuvant analgesia and symptomatic treatment of cord compression or raised intracranial pressure, dexamethasone 3.3mg/ml solution for injection may be administered subcutaneously (see section 4.2) as an alternative to the oral route when the latter is unacceptable or no longer feasible.

Local administration

Dexamethasone 3.3 mg/ml solution for injection is suitable for intraarticular or soft-tissue injection as adjunctive therapy for short-term administration in:

Soft-tissue disorders

Such as carpal tunnel syndrome and tenosynovitis

Intraarticular disorders

Such as rheumatoid arthritis and osteoarthritis with an inflammatory component

Dexamethasone 3.3 mg/ml solution for injection may be injected intralesionally in selected skin disorders such as cystic acne vulgaris, localised lichen simplex, and keloids.

4.2 Posology and method of administration

Posology

*All dosage recommendations are given in units of dexamethasone **base.***

General considerations

Dosage must be individualised on the basis of the disease and the response of the patient. In order to minimise side effects, the lowest possible dosage adequate to control the disease process should be used (see section 4.8).

Intravenous and intramuscular injection

Usually the parenteral dosage ranges are one-third to one-half of the oral dose, given every 12 hours.

The usual initial dosage is 0.4 mg – 16.6 mg (0.12 ml – 5.0 ml) a day. In situations of less severity, lower doses will generally suffice. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosage may be justified. In these circumstances, the slower rate of absorption by intramuscular administration should be recognised.

Both the dose in the evening, which is useful in alleviating morning stiffness and the divided dosage regimen are associated with greater suppression of the hypothalamo-pituitary-adrenal axis. After a favourable response is noted, the proper maintenance dosage should be determined by decreasing the initial dosage by small amounts at appropriate intervals to the lowest dosage which will maintain an adequate clinical response. Chronic dosage should preferably not exceed 500 micrograms dexamethasone daily. Close monitoring of the drug dosage is needed.

To avoid hypoadrenalism and/or a relapse of the underlying disease, it may be necessary to withdraw the drug gradually (see 'Special warnings and precautions for use').

Whenever possible, the intravenous route should be used for the initial dose and for as many subsequent doses as are given while the patient is in shock (because of the irregular rate of absorption of any medicament administered by any other route in such patients). When the blood pressure responds, use the intramuscular route until oral therapy can be substituted. For the comfort of the patient, not more than 2 ml should be injected intramuscularly at any one site.

In emergencies, the usual dose of Dexamethasone 3.3 mg/ml solution for injection by intravenous or intramuscular injection is 3.3 mg – 16.6 mg (1.0 ml – 5.0 ml) - in shock use only the i.v. route. This dose may be repeated until adequate response is noted.

After initial improvement, single doses of 1.7 mg – 3.3 mg (0.5 ml – 1.0 ml), repeated as necessary, should be sufficient. The total daily dosage usually need not exceed 66.4 mg (20.0 ml), even in severe conditions.

When constant maximal effect is desired, dosage must be repeated at three-hour or four-hour intervals or maintained by slow intravenous drip.

Intravenous or intramuscular injections are advised in acute illness. When the acute stage has passed, oral steroid therapy should be substituted as soon as feasible.

For the treatment of COVID-19

Adult patients 6 mg (1.8ml) IV, once a day for up to 10 days.

Paediatric population

Paediatric patients (adolescents aged 12 years and older) are recommended to be given a 6mg dose (1.8ml) IV 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.

Shock (of haemorrhagic, traumatic, or surgical origin):

Usually 1.7 mg – 5.0 mg/kg (0.5 ml – 1.5 ml/kg) bodyweight as a single intravenous injection. This may be repeated in two to six hours if shock persists. Alternatively, this may be followed immediately by the same dose in an intravenous

infusion. Therapy with Dexamethasone 3.3 mg/ml solution for injection is an adjunct to and not a replacement for conventional therapy.

Administration of these high doses should be continued only until the patient's condition has stabilised and usually no longer than 48-72 hours.

Cerebral oedema:

• *Management of recurrent or inoperable brain tumours:*

Maintenance therapy should be determined for each patient; 1.7 mg (0.5 ml) two or three times a day may be effective. The smallest dose necessary to control cerebral oedema should be used.

• *Cerebral oedema associated with primary or metastatic brain tumour, preoperative preparation of patients with increased intracranial pressure secondary to brain tumour:*

Initially 8.3 mg (2.5ml) intravenously, followed by 3.3 mg (1.0 ml) intramuscularly every six hours until symptoms of cerebral oedema subside. Response is usually noted within 12-24 hours; dosage may be reduced after two to four days and gradually discontinued over five to seven days.

High doses of Dexamethasone 3.3 mg/ml solution for injection are recommended for initiating short-term intensive therapy for acute life-threatening cerebral oedema. Following the high-loading dose schedule of the first day therapy, the dose is scaled down over the seven- to ten- day period of intensive therapy and subsequently reduced to zero over the next seven to ten days. When maintenance therapy is required, substitute oral dexamethasone as soon as possible (see table below).

Suggested high-dose schedule in cerebral oedema	
Adults	
Initial dose 41.5 mg dexamethasone (12.5 ml) i.v.	
1st day	6.6 mg dexamethasone (2.0 ml) i.v. every 2 hours
2nd day	6.6 mg dexamethasone (2.0 ml) i.v. every 2 hours
3rd day	6.6 mg dexamethasone (2.0 ml) i.v. every 2 hours
4th day	3.3 mg dexamethasone (1.0 ml) i.v. every 2 hours
5th-8th days	3.3 mg dexamethasone (1.0 ml) i.v. every 4 hours
Thereafter	decrease by daily reduction of 3.3 mg dexamethasone (1.0 ml)
Children (35 kg and over)	
Initial dose 20.8 mg dexamethasone (6.25 ml) i.v.	
1st day	3.3 mg dexamethasone (1.0 ml) i.v. every 2 hours
2nd day	3.3 mg dexamethasone (1.0 ml) i.v. every 2 hours
3rd day	3.3 mg dexamethasone (1.0 ml) i.v. every 2 hours
4th day	3.3 mg dexamethasone (1.0 ml) i.v. every 4 hours
5th-8th days	3.3 mg dexamethasone (1.0 ml) i.v. every 6 hours
Thereafter	decrease by daily reduction of 1.7 mg dexamethasone (0.5 ml)
Children (below 35 kg)	
Initial dose 16.6 mg dexamethasone (5.0 ml) i.v.	
1st day	3.3 mg dexamethasone (1.0 ml) i.v. every 3 hours

2nd day	3.3 mg dexamethasone (1.0 ml) i.v. every 3 hours
3rd day	3.3 mg dexamethasone (1.0 ml) i.v. every 6 hours
4th day	3.3 mg dexamethasone (1.0 ml) i.v. every 3 hours
5th-8th days	1.7 mg dexamethasone (0.5 ml) i.v. every 6 hours
Thereafter	decrease by daily reduction of 0.83 mg dexamethasone (0.25 ml)

Dual therapy to treat hypersensitivity reactions:

In acute self-limiting allergic disorders or acute exacerbations of chronic allergic disorders, the following schedule combining oral and parenteral therapy is suggested:

First day:	Dexamethasone 3.3 mg/ml solution for injection, 3.3 mg – 6.6 mg (1.0 ml – 2.0 ml) intramuscularly
Second day	Two 500 microgram dexamethasone tablets twice a day
Third day:	Two 500 microgram dexamethasone tablets twice a day
Fourth day:	One 500 microgram dexamethasone tablet twice a day
Fifth day:	One 500 microgram dexamethasone tablet twice a day
Sixth day:	One 500 microgram dexamethasone tablet once daily
Seventh day:	One 500 microgram dexamethasone tablet once daily
Eighth day:	Reassessment day

Subcutaneous administration

In palliative care, subcutaneous Dexamethasone 3.3 mg/ml solution for injection may be administered by injection or Continuous Subcutaneous Infusion (CSCI). Doses usually range between 4 mg to 16 mg over 24 hours, taking into consideration local clinical guidelines, and should be titrated according to the response.

Intraarticular, intrabursal or intralesional injection

In general, these injections are employed when only one or two joints or areas are affected.

Some of the usual single doses are:

SITE OF INJECTION	DEXAMETHASONE DOSE
Large joint (e.g. knee)	1.7 mg – 3.3 mg (0.5 ml – 1.0 ml)
Small joints (e.g. interphalangeal, temporomandibular)	0.66 mg – 0 .8 mg (0.2 ml – 0.25 ml)
Bursae	1.7 mg – 2 .5 mg (0.5 ml – 0.75 ml)
Tendon sheaths*	0.33 mg – 0.8 mg (0.1 ml – 0.25 ml)
Soft-tissue infiltration	1.7 mg – 5.0 mg (0.5 ml – 1.5 ml)
Ganglia	0.8 mg – 1.7 mg (0.25 ml – 0.5 ml)

*Injection should be made into the tendon sheath and not directly into the tendon.

Frequency of injection: once every three to five days to once every two to three weeks, depending on response.

Use in special population groups

Paediatric population

• *Neonates*

Any decision to use Dexamethasone 3.3mg/ml solution for injection in this population should be made on a case-by-case basis and following a careful assessment of the potential benefits and risks of treatment (see section 4.4).

• *Infants and children younger than 5 years old*

Dexamethasone 3.3 mg/ml solution for injection contains propylene glycol (20 mg per ml). The product should therefore be used with **caution** in infants and children younger than 5 years old when high doses of dexamethasone are required (see section 4.4).

Where possible, administration should be limited to a single dose on alternate days to lessen retardation of growth and minimise suppression of the hypothalamo-pituitary adrenal axis.

Use in patients with hepatic or renal impairment

Due to the presence of excipient propylene glycol, medical monitoring is required in patients with impaired hepatic or renal function when Dexamethasone 3.3 mg/ml solution for injection is administered at doses above 8.5 mg/kg/day (equivalent to 50 mg/kg/day propylene glycol) – see section 4.4.

Use in the elderly:

Treatment of elderly patients, particularly if long term, should be planned bearing in mind the more serious consequences of the common side effects of corticosteroids in old age, especially osteoporosis, diabetes, hypertension, hypokalaemia, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life threatening reactions (see section 4.8).

Method of administration

Dexamethasone 3.3 mg/ml solution for injection can be given without mixing or dilution. Alternatively, it can be added, without loss of potency, to sodium chloride, or dextrose, injection and given by intravenous infusion.

In palliative care, Dexamethasone 3.3mg/ml solution for injection can be diluted with sodium chloride injection and given by Continuous Subcutaneous Infusion (CSCI). Infusion mixtures must be used within 24 hours and the usual aseptic techniques for injections should be observed.

4.3 Contraindications

Systemic fungal infection; systemic infection unless specific anti-infective therapy is employed; hypersensitivity to the active ingredient or any other component of this medication. Administration of live virus vaccines (see 'Special warnings and precautions for use').

4.4 Special warnings and precautions for use

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.

Patients/and or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5 pharmacokinetic interactions that can increase the risk of side effects), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover 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. Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

Frequent intraarticular injections over a prolonged period may lead to joint destruction with bone necrosis. Intraarticular injection of corticosteroid may produce systemic adverse reactions including adrenal suppression.

Undesirable effects may be minimised by using the lowest effective dose for minimum period. Frequent patient review is required to appropriately titrate the dose against disease activity. When reduction in dosage is possible, the reduction should be gradual (see 'Posology and method of administration').

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.

Corticosteroids may exacerbate systemic fungal infections and, therefore, should not be used in the presence of such infections, unless they are needed to control drug reactions due to amphotericin. Moreover, there have been cases reported in which, concomitant use of amphotericin and hydrocortisone, was followed by cardiac enlargement and congestive failure.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, retention of salt and water and increased excretion of potassium, but these effects are less likely to occur with synthetic derivates, except when used in large doses. Dietary salt restrictions and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

The slower rate of absorption by intramuscular administration should be recognised.

In patients on corticosteroid therapy subjected to unusual stress (e.g. intercurrent illness, trauma or surgical procedures), dosage should be increased before, during and after the stressful situation. Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimised by gradual dosage reduction, being tapered off over weeks and months, depending on the dose and duration of treatment, but may persist for up to a year after discontinuation of therapy. In any stressful situation during that period, therefore, corticosteroid therapy should be reinstated. If the patient is already receiving corticosteroids, the current dosage may have to be temporarily increased. Salt and/or a mineralocorticoid should be given concurrently, since mineralocorticoid secretion may be impaired.

Stopping corticosteroids after prolonged therapy may cause withdrawal symptoms, including fever, myalgia, arthralgia and malaise. This may occur in patients even without evidence of adrenal insufficiency.

In patients who have received more than physiological doses of systemic corticosteroids (approximately 1 mg dexamethasone) for greater than three weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. 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 hypothalamic-pituitary adrenal (HPA) suppression, the dose of systemic corticosteroids *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.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to three 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 three weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be *considered* even after courses lasting three weeks or less:

• patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than three weeks,

• when a short course has been prescribed within one year of cessation of long-term therapy (months or years),

• patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy,

• patients receiving doses of systemic corticosteroid greater than 6 mg daily of dexamethasone,

• patients repeatedly taking doses in the evening.

Patients should carry 'steroid treatment' cards, which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and the duration of treatment.

Because anaphylactoid reactions have occurred, rarely, in patients receiving parenteral corticosteroid therapy, appropriate precautions should be taken prior to administration, especially when the patient has a history of allergy to any drug.

Administration of live virus vaccines is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained. However, immunisation procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g. for Addison's disease.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

The use of Dexamethasone 3.3 mg/ml solution for injection in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in

conjunction with an appropriate antituberculosis regimen. If the corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation may occur. During prolonged corticosteroid therapy, these patients should receive prophylactic chemotherapy.

Corticosteroids may mask some signs of infection and new infections may appear during their use. Suppression of the inflammatory response and immune function increasing the susceptibility to infections and their severity. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked and reach an advanced stage before being recognised. There may be decreased resistance and inability to localise infection.

A report shows that the use of corticosteroids in cerebral malaria is associated with a prolonged coma and an increased incidence of pneumonia and gastro-intestinal bleeding.

Chickenpox is of particular concern, since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunisation with varicella/zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous three month; this should be given within ten days of exposure to chickenpox.

If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

Measles can have a more serious or even fatal course in immunosuppressed patients. In such children or adults particular care should be taken to avoid exposure to measles. If exposed, prophylaxis with intramuscular pooled immunoglobulin (IG) may be indicated. Exposed patients should be advised to seek medical advice without delay.

Corticosteroids may activate latent amoebiasis or strongyloidiasis or exacerbate active disease. Therefore, it is recommended that latent or active amoebiasis and strongyloidiasis be ruled out, before initiating corticosteroid therapy in any patient at risk of or with symptoms of either condition.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Corticosteroids may increase or decrease motility and number of spermatozoa.

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.

Special precautions:

Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary: renal insufficiency and liver failure (see *Propylene glycol content*, below), hypertension, diabetes or in those with a family history of diabetes, congestive heart failure, osteoporosis, previous steroid myopathy, glaucoma (or family history of glaucoma), myasthenia gravis, non-specific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, existing or previous history of severe affective disorders (especially previous steroid psychosis), and epilepsy. Signs of peritoneal irritation, following gastrointestinal perforation in patients receiving large doses of corticosteroids, may be minimal or absent. Fat embolism has been reported as a possible complication of hypercortisonism.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

Local steroid injection should be undertaken in an aseptic environment to reduce the particular risk of bacterial infection, injection of a steroid into an infected site should be avoided.

Appropriate examination of joint fluids is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Patients should understand the great importance of not over-using joints that are still diseased, despite symptomatic improvement.

Corticosteroids should not be injected into unstable joints.

Frequent intraarticular injections have been reported to cause development of Charcot-like arthropathies.

<u>Paediatric population</u>

Neonates:

Dexamethasone has been used to treat and prevent bronchopulmonary dysplasia (formerly known as chronic lung disease) in preterm neonates (unlicensed use). Clinical trials have shown no long-term benefit in reducing time to discharge, the incidence of chronic lung disease or mortality. Recent trials have suggested an association between the use of dexamethasone in preterm neonates and the development of cerebral palsy. Available evidence suggests long-term neurodevelopmental adverse events after early treatment (< 96 hours) of premature infants in this indication at starting doses of 0.25mg/kg twice daily. In view of these safety concerns, any decision to use Dexamethasone 3.3 mg/ml solution for injection in this population should be made on a case-by-case basis and following a careful assessment of the potential benefits and risks of treatment . Any benefit-risk assessment of the use of Dexamethasone 3.3 mg/ml solution for injection in this population should take into account the propylene glycol content of the product – see *Propylene glycol content*, below.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy was reported after systemic administration of corticosteroids including dexamethasone to prematurely born infants. In the majority of cases reported, this was reversible on withdrawal of treatment. In preterm infants treated with systemic dexamethasone diagnostic evaluation and monitoring of cardiac function and structure should be performed (section 4.8).

Children:

Corticosteroids cause growth retardation in infancy, childhood and adolescence, which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time. In order to minimise suppression of the hypothalamo-pituitary-adrenal axis and growth retardation, treatment should be limited, where possible, to a single dose on alternate days.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully monitored.

Dexamethasone 3.3 mg/ml solution for injection should be used with **caution** in infants and children younger than 5 years old when high doses are required – see *Propylene glycol content*, below.

Propylene glycol content

Dexamethasone 3.3 mg/ml solution for injection contains propylene glycol (20 mg per ml). The following population groups are particularly at risk of developing propylene glycol toxicity:

• *Neonates*

In neonates, a safety threshold of 1mg/kg/day has been set for excipient propylene glycol by the European Medicines Agency (corresponding to a 0.17 mg/kg/day dose of Dexamethasone 3.3 mg/ml solution for injection) Exceeding this threshold may induce serious adverse effects in this population when co-administered with any substrate for alcohol dehydrogenase such as ethanol. The potential for propylene glycol toxicity should therefore be considered as part of any benefit-risk assessment of the use of Dexamethasone 3.3 mg/ml solution for injection in this population – see *Paediatric population*, above. Any use of the product in this population would require close medical monitoring.

• *Infants and children younger than 5 years old*

In infants and children younger than 5 years old, a safety threshold of 50 mg/kg/day has been set for excipient propylene glycol by the European Medicines Agency (corresponding to an 8.5 mg/kg/day dose of Dexamethasone 3.3 mg/ml solution for injection). When high doses of Dexamethasone 3.3 mg/ml solution for injection are required (e.g. for the treatment of life-threatening cerebral oedema– see section 4.2), the corresponding propylene glycol exposure may exceed the 50 mg/kg/day threshold in some patients from this population. The co-administration of propylene glycol at or above this safety threshold with any substrate for alcohol dehydrogenase (such as ethanol) may induce adverse effects in children younger than 5 years old. Dexamethasone 3.3 mg/ml solution for injection should therefore be used with **caution** in this population when the product is used in high doses.

• *Patients with hepatic or renal impairment*

Various adverse events attributable to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure, and liver dysfunction. Medical monitoring in this population is required when Dexamethasone 3.3 mg/ml solution for injection is administered at doses of 8.5 mg / kg / day (equivalent to 50 mg / kg / day propylene glycol) and above.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per each 1 ml and 2 ml ampoule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinaemia.

The renal clearance of salicylates is increased by corticosteroids and therefore salicylate dosage should be reduced along with steroid withdrawal.

As phenytoin, barbiturates, ephedrine, rifabutin, carbamazepine, rifampicin and aminoglutethimide may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and reduced physiological activity, the dosage may have to be adjusted. These interactions interfere with dexamethasone suppression tests which should be interpreted with caution during administration of these drugs.

False-negative results in the dexamethasone suppression test in patients being treated with indometacin have been reported.

The efficacy of coumarin anticoagulants may be changed by concurrent corticosteroid treatment. The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time, in order to avoid spontaneous bleeding.

The desired effects of hypoglycaemic agents (including insulin) are antagonised by corticosteroids.

When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalaemia.

Corticosteroids may affect the nitroblue tetrazolium test for bacterial infection and produce false-negative results.

Antiretroviral protease inhibitors (ritonavir, darunavir, indinavir, lopinavir, saquinavir and efavirenz) are metabolised by CYP3A. Medicinal products that induce CYP3A activity, such as dexamethasone, may increase the clearance of medicines metabolised by CYP3A, resulting in lowered plasma concentrations.

Certain antiretroviral protease inhibitors (ritonavir, indinavir) may also be inhibitors of CYP3A themselves and as a result may increase the plasma concentration of dexamethasone.

4.6 Fertility, pregnancy and lactation

Pregnancy

The ability of corticosteroids to cross the placenta varies between individual drugs, however, dexamethasone readily crosses the placenta.

Studies have shown an increased risk of neonatal hypoglycaemia following antenatal administration of a short course of corticosteroids including dexamethasone to women at risk for late preterm delivery.

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.

However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intrauterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in non-gravid state.

Lactation

Corticosteroids may pass into breast milk, although no data are available for dexamethasone. Infants of mothers taking high doses of systemic corticosteroids for prolonged periods may have a degree of adrenal suppression.

4.7 Effects on ability to drive and use machines

None reported

4.8 Undesirable effects

The incidence of predictable undesirable effects, including hypothalamic-pituitary-adrenal suppression, correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see 'Special warnings and precautions for use').

Fluid and electrolyte disturbances:

Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalaemic alkalosis, hypertension, increased calcium excretion (see 'Special warnings and precautions for use')

Musculoskeletal:

Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis (especially in post-menopausal females), vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathological fracture of long bones, tendon rupture and post-injection flare (following intraarticular use')

Gastrointestinal:

Peptic ulcer with possible perforation and haemorrhage, perforation of the small and large bowel, particularly in patients with inflammatory bowel disease, pancreatitis, abdominal distension, ulcerative oesophagitis, dyspepsia, oesophageal candidiasis

Dermatological:

Impaired wound healing, thin fragile skin, petechiae and ecchymoses, erythema, striae, telangiectasia, acne, increased sweating, possible suppression of skin tests, burning or tingling especially in the perineal area (after intravenous injection), other cutaneous reactions such as allergic dermatitis, urticaria, angioneurotic oedema and hypo- or hyper-pigmentation

Neurological:

Convulsions, increased intracranial pressure with papilloedema (pseudotumour cerebri) usually after treatment, vertigo, headache, cerebral palsy in pre-term infants

Psychiatric:

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 are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown.

Endocrine:

Menstrual irregularities, amenorrhoea, development of Cushingoid state, suppression of growth in children and adolescents, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress as in trauma, surgery or illness), decreased carbohydrate tolerance, manifestation of latent diabetes mellitus, increased requirements for insulin or oral hypoglycaemic agents in diabetes, hirsutism

Anti-inflammatory and immunosuppressive effects:

Increased susceptibility and severity of infections with suppression of clinical symptoms and signs; opportunistic infections, recurrence of dormant tuberculosis (see 'Special warnings and precautions for use')

Ophthalmic:

Posterior subcapsular cataracts, increased intraocular pressure, papilloedema, corneal or scleral thinning, exacerbation of ophthalmic viral disease, glaucoma exophthalmos, rare instances of blindness associated with intralesional therapy around the face and head, retinopathy of prematurity, chorioretinopathy.

Metabolic:

Negative nitrogen balance due to protein catabolism, negative calcium balance

Cardiovascular:

Myocardial rupture following recent myocardial infarction (see 'Special warnings and precautions for use'), hypertrophic cardiomyopathy in prematurely born infants (see section 4.4).

Other:

Hypersensitivity, including anaphylaxis has been reported, leucocytosis, thrombo-embolism, weight gain, increased appetite, nausea, malaise, hiccups and sterile abscess.

Multiple myeloma patients treated with lenalidomide or thalidomide in combination with dexamethasone have an increased risk of thromboembolic events including deep vein thrombosis and pulmonary embolism.

Withdrawal symptoms and signs

Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see 'Special warnings and precautions for use')

In some instances, withdrawal symptoms may simulate a clinical relapse of the disease for which the patient has been undergoing treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Reports of acute toxicity and/or deaths following overdosage with glucocorticoids are rare. No antidote is available. Treatment is probably not indicated for reactions due to chronic poisoning, unless the patient has a condition that would render a patient unusually susceptible to ill effects from corticosteroids. In this case, symptomatic treatment should be instituted as necessary.

Anaphylactic and hypersensitivity reactions may be treated with adrenaline, positive-pressure artificial respiration and aminophylline. The patient should be kept warm and quiet.

The biological half-life of dexamethasone in plasma is about 190 minutes.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids

ATC code: H02AB02

Dexamethasone possesses the actions and effects of other basic glucocorticoids and is among the most active members of its class.

Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. They cause profound and varied metabolic effects and in addition, they modify the body's immune responses to diverse stimuli. Naturally-occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used primarily for their potent anti-inflammatory effects in disorders of many organ systems.

Dexamethasone has predominant glucocorticoid activity with little propensity to promote renal retention of sodium and water. Therefore it does not offer complete replacement therapy and must be supplemented with salt or desoxycorticosterone.

Clinical efficacy and safety – COVID-19

Clinical efficacy

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)** *no./total no. of patients (%)*	**Rate or Risk Ratio (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 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.

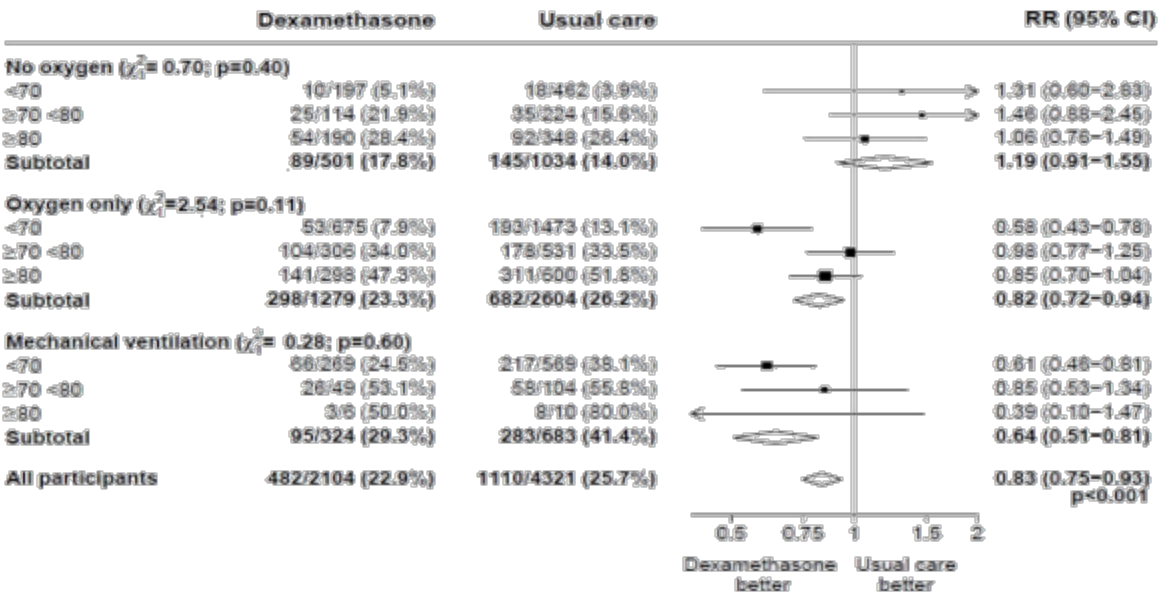
† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.

Safety

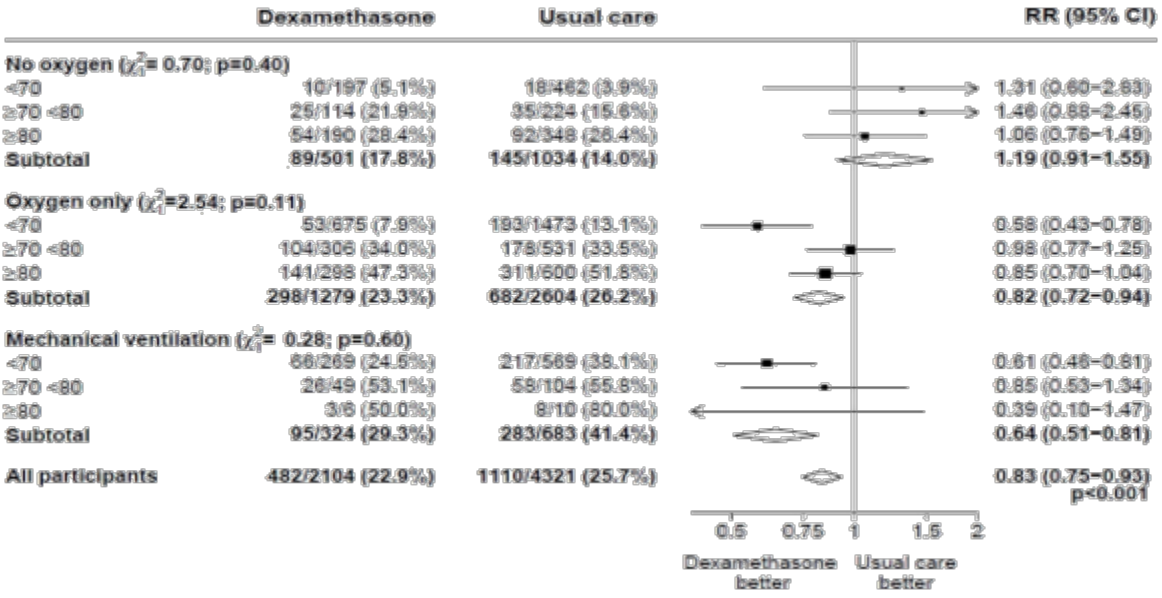
There were four serious adverse events (SAEs) related to study treatment: two SAEs of hyperglycaemia, one SAE of steroid-induced psychosis and one SAE of an upper gastrointestinal bleed. All events resolved.

Subgroup analyses

Effects of allocation to DEXAMETHASONE on 28−day mortality, by respiratory support received at randomisation and history of any chronic disease[2].



Effects of allocation to DEXAMETHASONE on 28−day mortality, by age and respiratory support received at randomisation[2]



[1] www.recoverytrial.net

[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

The biological half-life of dexamethasone in plasma is about 190 minutes.

Binding of dexamethasone to plasma proteins is less than for most other corticosteroids and is estimated to be about 77%.

Up to 65% of a dose is excreted in the urine in 24 hours, the rate of excretion being increased following concomitant administration of phenytoin.

The more potent halogenated corticosteroids such as dexamethasone, appear to cross the placental barrier with minimal inactivation.

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

Propylene glycol,

disodium edetate,

sodium hydroxide solution

Water for Injections.

6.2 Incompatibilities

Dexamethasone is physically incompatible with daunorubicin, doxorubicin, vancomycin, diphenhydramine (with lorazepam and metoclopramide) and metaraminol bitartrate and should not be admixed with solutions containing these drugs. It is also incompatible with doxapram and glycopyrrolate in syringe and with ciprofloxacin, idarubicin and midazolam in Y-site injections (1:1 mixture).

6.3 Shelf life

2 years.

From a microbiological point of view, the product should be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 h at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Any unused portion of the product should be discarded immediately after use.

Chemical and physical in-use stability of dilutions has been demonstrated for 24 h at 25°C. Dilutions should be used within 24 hours and discarded after use.

6.4 Special precautions for storage

Keep container in the outer carton.

Do not freeze.

Store below 25°C.

Any unused portion should be discarded immediately after use.

6.5 Nature and contents of container

Type I clear glass ampoule containing 1 ml solution for injection.

Type I clear glass ampoule containing 2 ml solution for injection.

1 ml	**2 ml**
Package of 1 ampoule of 1 ml	Package of 1 ampoule of 2 ml
Package of 5 ampoules of 1 ml each	Package of 5 ampoules of 2 ml each
Package of 10 ampoules of 1 ml each	Package of 10 ampoules of 2 ml each

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When Dexamethasone 3.3 mg/ml solution for injection is given by intravenous infusion, dextrose 5% in water and sodium chloride 0.9% have been recommended as diluents. The exact concentration of dexamethasone per infusion container should be determined by the desired dose, patient fluid intake and drip rate required

7. Marketing authorisation holder

hameln pharma ltd

Nexus, Gloucester Business Park

Gloucester, GL3 4AG

United Kingdom

8. Marketing authorisation number(s)

PL 01502 /0079

9. Date of first authorisation/renewal of the authorisation

13/06/2006

10. Date of revision of the text

23/02/2022

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Appendix 3 – SmPC for Prednisolone 10mg tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Prednisolone 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg prednisolone.

Excipient with known effect
Each tablet contains 81.7mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

10mg tablet

Red, 7mm, round, flat, tablet, with a score line on one side, imprinted with “A630” on one side and “10” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Allergy and anaphylaxis: bronchial asthma, drug hypersensitivity reactions, serum sickness, angioneurotic oedema, anaphylaxis, incapacitating allergies unresponsive to conventional treatment.

Arteritis/collagenosis: giant cell arteritis/polymyalgia rheumatica, mixed connective tissue disease, polyarteritis nodosa, polymyositis.

Blood disorders: haemolytic anaemia (auto-immune), leukaemia (acute and chronic lymphocytic), lymphoma, multiple myeloma, idiopathic thrombocytopenic purpura.

Cardiovascular disorders: post-myocardial infarction syndrome, rheumatic fever with severe carditis.

Endocrine disorders: primary and secondary adrenal insufficiency, congenital adrenal hyperplasia.

Gastro-intestinal disorders: regional ileitis (Crohn's disease), ulcerative colitis, persistent coeliac syndrome (coeliac disease unresponsive to gluten withdrawal), auto-immune chronic active hepatitis, multisystem disease affecting liver, biliary peritonitis.

Hypercalcaemia: sarcoidosis, vitamin D excess.

Infections (with appropriate chemotherapy): helminthic infestations, Herxheimer reaction, infectious mononucleosis, miliary tuberculosis, mumps orchitis (adult), tuberculous meningitis, rickettsial disease.

Muscular disorders: polymyositis, dermatomyositis.

Neurological disorders: infantile spasms, Shy-Drager syndrome, sub-acute demyelinating polyneuropathy.

Ocular disease: scleritis, posterior uveitis, retinal vasculitis, pseudo-tumours of the orbit, giant cell arteritis, malignant ophthalmic Graves disease.

Renal disorders: lupus nephritis, acute interstitial nephritis, minimal change glomerulonephritis, nephrotic syndrome.

Respiratory disease: allergic pneumonitis, asthma, occupational asthma, pulmonary aspergillosis, pulmonary fibrosis, pulmonary alveolitis, aspiration of foreign body, aspiration of stomach contents, pulmonary sarcoid, drug induced lung disease, adult respiratory distress syndrome, spasmodic croup, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculosis chemotherapy.

Rheumatic disorders: rheumatoid arthritis, polymyalgia rheumatica, juvenile chronic arthritis, psoriatic arthritis, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease.

Skin disorders: pemphigus vulgaris, exfoliative dermatitis, bullous pemphigoid, systemic lupus erythematosus, pyoderma gangrenosum.

Miscellaneous: sarcoidosis, hyperpyrexia, Behçets disease, immunosuppression in organ transplantation.

4.2 Posology and method of administration

Posology

Adults and the elderly

The lowest effective dose should be used for the minimum period.

Children

Prednisolone should only be used when specifically indicated, at the lowest dose possible and for the shortest possible time.

The initial dosage of Prednisolone may vary from 5mg to 60mg daily depending on the disorder being treated. Divided daily dosage may be used. Administration as a once daily dose in the morning or on alternate days can reduce the risk of adrenocortical suppression (see Section 4.4 Special warnings and precautions for use). In some patients this may not be possible e.g. patients with rheumatoid arthritis with pronounced morning stiffness where an evening dose may need to be given.

The following therapeutic guidelines should be kept in mind for all therapy with corticosteroids:

The lowest dose to produce an acceptable result should be given. Initial dosage should be adjusted until the desired clinical response has been achieved. The dose should be gradually reduced until the lowest dose which will maintain an adequate clinical response is reached. As a guide, the daily dose should be reduced by 2.5 – 5 mg every second to fifth day (more rapidly at the higher initial dose levels) until the lowest possible maintenance dose is reached. Preferably this should not exceed 10 mg per day. Use of the lowest effective dose will tend to minimise side-effects. The incidence of side-effects increases with dose and duration of treatment (see Section 4.4 'Special warnings and special precautions for use').

Particular care should be exercised in patients who have received higher than 7.5mg prednisolone daily or equivalent for more than 3 weeks, owing to a greater risk of suppression of the hypothalamic-pituitary-adrenal (HPA) axis in these patients. The speed with which dose can be reduced is also dependent on risk of relapse of the disease being treated. After prolonged treatment, tapering of dose below 7.5 mg (regarded as “equivalent” to physiological levels of glucocorticoids) should be conducted particularly cautiously.

More rapid withdrawal of systemic corticosteroid treatment that has been given for less than 3 weeks is appropriate if it is considered that the disease is unlikely to relapse. Withdrawal of doses of up to 40mg daily of prednisolone, or equivalent that have been administered for less than 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. 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 if taken for greater than 3 weeks.
- when a short course has been prescribed within one year of cessation of long-term therapy (months or years).
- patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
- patients receiving doses of systemic corticosteroid greater than 40mg daily of prednisolone (or equivalent).
- patients repeatedly taking doses in the evening.

(See Section 4.4 'Special warnings and special precautions for use' and Section 4.8 'Undesirable effects')

During prolonged therapy, dosage may need to be temporarily increased during periods of stress or during exacerbations of the disease (see Section 4.4 'Special warnings and special precautions for use')

If there is lack of a satisfactory clinical response to Prednisolone Tablets, the drug should be gradually discontinued and the patient transferred to alternative therapy.

Intermittent dosage regimen A single dose of PrednisoloneTablets in the morning on alternate days or at longer intervals is acceptable therapy for some patients. When this regimen is practical, the degree of pituitary-adrenal suppression can be minimised.

Specific dosage guidelines The following recommendations for some corticosteroid-responsive disorders are for guidance only. Acute or severe disease may require initial high dose therapy with reduction to the lowest effective maintenance dose as soon as possible. Dosage reductions should not exceed 5-7.5mg daily during chronic treatment.

Allergic and skin disorders Initial doses of 5-15mg daily are commonly adequate.

Collagenosis Initial doses of 20-30mg daily are frequently effective. Those with more severe symptoms may require higher doses.

Rheumatoid arthritis The usual initial dose is 10-15mg daily. The lowest daily maintenance dose compatible with tolerable symptomatic relief is recommended.

Blood disorders and lymphoma An initial daily dose of 15-60mg is often necessary with reduction after an adequate clinical or haematological response. Higher doses may be necessary to induce remission in acute leukaemia.

Special populations

Use in elderly Treatment of elderly patients, particularly if long-term, should be undertaken with caution bearing in mind the more serious consequences of the common side-effects of corticosteroids in old age (see also 'Special warnings and special precautions for use').

Use in children: Although appropriate fractions of the adult dose may be used, dosage will usually be determined by clinical response as in adults (see also Section 4.4 'Special warnings and special precautions for use' and Section 4.8 'Undesirable effects'). Alternate day dosage is preferable where possible.

Method of administration

Prednisolone tablets should be taken following a meal to reduce the risk of gastric irritation.

4.3 Contraindications

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

Administration of live vaccines is contraindicated in patients receiving corticosteroids in immunosuppressive doses.

In those conditions when treatment with prednisolone can save lives, none of the contraindications generally applies.

4.4 Special warnings and precautions for use

Since the complications of glucocorticoid therapy are dependent on the dose and duration of treatment, a risk / benefit assessment must be made in each case regarding dose and duration of treatment, as well as whether daily or intermittent treatment should be used.

The lowest possible corticosteroid dose needed to control the disease being treated should be used. When dose reduction is possible, it should be gradual.

Immunosuppressive effects / increased infection sensitivity
Glucocorticoids, including prednisolone, may cause increased susceptibility to infection, masking symptoms of infection, and new infections may occur during treatment.
Infections caused by viruses, bacteria, fungi, protozoa or helminths may be associated with the use of corticosteroids alone or corticosteroids in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity or the function of neutrophils. The infections can be mild, but also difficult and in some cases fatal. The risk of infectious complications increases with increasing dose.

Glucocorticoids should not be given during infections without concomitant causal treatment.

Chickenpox and measles can be more serious or even fatal in non-immunized children and adults treated with corticosteroids. Children, or adults who have not had these diseases, and who take immunosuppressive doses of corticosteroids, should be advised to avoid exposure to chickenpox and measles, and to seek care when exposed.
The use of prednisolone in active tuberculosis should be limited to those cases of fulminant or disseminated tuberculosis where the corticosteroid is used to treat the disease in combination with appropriate tuberculosis therapy. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, careful monitoring is necessary as the disease can be reactivated. In long-term corticosteroid therapy, these patients should receive tuberculosis prophylaxis.

High dose corticosteroids may interfere with active immunization.

Vaccination with live vaccine should be done under close supervision and not in patients on long-term treatment with corticosteroids in immunosuppressive doses.

Immune system
Since rare cases of skin reactions and anaphylactic / anaphylactoid reactions have occurred in patients treated with corticosteroids, appropriate precautions should be taken prior to administration, especially if the patient has previously had an allergic reaction to any drug.

Endocrine system

Long-term treatment with pharmacological doses of corticosteroid may lead to secondary adrenal insufficiency. The risk can be reduced by giving the treatment every other day (see section 4.2).

Patients who receive corticosteroid maintenance therapy and are exposed to unusual stresses (e.g. infection, surgery or trauma) need higher corticosteroid doses before, during and after the stressful situation.

Abrupt termination of treatment may lead to acute adrenal insufficiency which may be fatal. The risk of secondary adrenal insufficiency can be reduced by gradually decreasing the dose. This type of relative insufficiency may persist for months after the end of treatment, so hormone replacement therapy should be reintroduced in stressful situations occurring during this time period. Since the secretion of mineral corticoids may be impaired, salts and / or mineral corticoids should be administered simultaneously.

A "steroid withdrawal syndrome", apparently without associated with adrenal insufficiency, may also occur following abrupt withdrawal of glucocorticoids. This syndrome causes symptoms such as anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss and / or hypotension. These effects are believed to be due to the sudden change in glucocorticosteroid concentration rather than to low corticosteroid levels.

Patients with hypothyroidism or liver cirrhosis will have an enhanced effect of corticosteroids.

Pheochromocytoma-related crisis, which may be fatal, has been reported following systemic corticosteroid administration. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma following consideration of individual risk / benefit.

Metabolism and nutrition
Corticosteroids, including prednisolone, can raise blood sugar levels, exacerbate existing diabetes and increase the risk of developing diabetes in patients on long-term corticosteroid therapy.

Mental disorders
Potentially serious mental disorders may occur during treatment with corticosteroids including prednisolone. It can be anything from euphoria, sleep disorders, mood swings, personality changes and severe depression to psychotic manifestations. Existing emotional instability and psychotic tendencies can also be exacerbated by corticosteroids (see section 4.8). The symptoms typically begin within a few days or weeks after the start of treatment. Most reactions return after dose reduction or withdrawal, but specific treatment may be necessary.
Psychiatric effects have been reported with the withdrawal of corticosteroids, the frequency is unknown. Patients / caregivers should be encouraged to seek medical care if the patient shows mental symptoms, especially if depression or suicidal thoughts are suspected. Patients / caregivers should be aware that

mental disorders may occur either during or immediately after dose reduction / discontinuation of systemic steroids.

Central and peripheral nervous system
Corticosteroids should be used with caution in patients with seizures.

Heart
Side effects of glucocorticoids on the cardiovascular system, for example dyslipidemia and hypertension, can predispose in treated patients with existing cardiovascular risk factors for additional cardiovascular events at high doses and prolonged treatment times. Corticosteroids should therefore be introduced to these patients only after careful consideration, and risk-modifying measures as well as extra cardiac monitoring should be considered as needed. Low dose and treatment every other day can reduce the complications of corticosteroid treatment.

Blood vessels
Since cortisone has been reported to increase the blood clotting tendency in rare cases, thereby accelerating the development of intravascular thrombosis, thromboembolism and thrombophlebitis, corticosteroids should be used with caution in patients with thromboembolic disorders.

Gastrointestinal tract
High doses of corticosteroids can cause acute pancreatitis.
There are no conclusive data that states that corticosteroids cause ulcers. Glucocorticoid therapy can mask peritonitis and other signs and symptoms associated with gastrointestinal conditions such as perforation, obstruction or pancreatitis. In combination with NSAIDs, the risk of gastrointestinal ulcers is increased.
Corticosteroids should therefore be used with caution in non-specific ulcerative colitis if there is a likelihood of imminent perforation, abscess or other pyogenic infection, diverticulitis, newly created anastomoses, or active or latent peptic ulcer.

Liver and biliary tract
Diseases of the liver and bile ducts have been reported rarely and in the majority of these cases the condition was reversible after discontinuation of treatment. Appropriate monitoring measures are required.

Musculoskeletal system
Acute myopathy has been reported with high corticosteroid doses, most often in patients with neuromuscular transmission disorders (e.g., myasthenia gravis), or in patients concomitantly treated with anticholinergics, e.g. neuromuscular blocking drugs (such as pancuronium) (see section 4.5). This acute myopathy is generalized, may involve eye and respiratory muscles, and may lead to tetraparesis. Elevated creatine kinase may occur. Clinical improvement or recovery after discontinuation of corticosteroid therapy may take weeks or years.

Corticosteroids should be used with caution in patients with osteoporosis.

Kidneys and urinary tract
Corticosteroids should be used with caution in patients with renal insufficiency.

Acute renal crisis (renal crisis in scleroderma)
Caution is required in patients with systemic sclerosis as an increased incidence of (possibly fatal) renal crisis in scleroderma, with hypertension and decreased urine output, has been observed with a daily prednisolone dose of 15 mg or more. Therefore, blood pressure and renal function (S-creatinine) should be routinely monitored. In case of suspected renal crisis, blood pressure should be kept under close control.

Effects on electrolytes and fluid balance
Systemic corticosteroids should be used with caution in patients with heart failure or hypertension. Medium and high doses of hydrocortisone or cortisone can lead to increased blood pressure, salt and water retention and increased potassium secretion. These effects are less likely with synthetic derivatives, except when used in high doses. Dietary restrictions with lower salt intake and potassium supplementation may be necessary.
All corticosteroids increase calcium excretion.

Eyes
Syncope disorder can be reported in systemic and topical use of corticosteroids. If a patient comes with symptoms such as blurred vision or other visual disturbances, consideration should be given to referring the patient to ophthalmologist for investigation of possible causes. These may include cataracts, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR), which have been reported following the use of systemic and topical corticosteroids.

Use in children
Corticosteroids cause growth inhibition in infants, children and adolescents, therefore avoid long-term treatment with pharmacological doses. If long-term treatment is required, the infant / child's growth and development should be closely monitored (see section 4.2). Infants and children who are on long-term corticosteroid therapy are at particular risk of developing elevated intracranial pressure.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations with Prednisolone Pfizer may require dose adjustment.

Phenobarbital, phenytoin, carbamazepine:
Phenobarbital (which is also the metabolite of primidone), phenytoin and carbamazepine alone and in combination, induces the metabolism of hydrocortisone, prednisolone and methylprednisolone (shown in children with asthma) with increased dose requirements as a result. The interaction probably applies to the whole group of glucocorticoids.

Non-steroidal anti-inflammatory drugs:
1) The incidence of gastrointestinal bleeding and ulceration may increase if corticosteroids are given with NSAIDs.
2) Corticosteroids may increase the clearance of high doses of acetylsalicylic acid, which may lead to lower salicylate levels in the serum. Salicylate levels in serum may increase upon discontinuation of corticosteroid therapy, which could lead to an increased risk of toxic effects of salicylate.

Diabetes drugs:
Glucocorticoids increase blood sugar levels. Patients with diabetes mellitus receiving concomitant insulin and / or oral hypoglycaemic agents may need to adjust the dose of such treatment.

Estrogens *(also oral contraceptives containing estrogens)*:
estrogens increase the concentration of transcortin. The effect of glucocorticoids that bind to transcortin can be enhanced and dose adjustments may be needed if estrogens are added or removed from a stable treatment regimen.

Potassium Reducing Agents:
Potassium-reducing diuretics (e.g., thiazides, furosemide, ethacrynic acid) and other drugs that reduce the amount of potassium such as amphotericin B, xanthines and beta2-agonists, may potentiate the potassium-lowering effect of glucocorticoids. Serum potassium should be closely monitored in patients receiving glucocorticoids and potassium reducing agents.

Rifampicin:
Rifampicin induces the microsomal oxidation of glucocorticoids (hydrocortisone, prednisolone, methylprednisolone). This leads to an increased steroid need during rifampicin treatment and reduced steroid need after such treatment.

Isoniazid:
Prednisolone also has a potential effect which results in increased acetylation rate and clearance of isoniazid.

Oral anticoagulants:
There are reports of altered effects of anticoagulants given concurrently with prednisolone. Prothrombin time (INR) should be monitored during treatment.

CYP3A inhibitors, including medicinal products containing cobicistat:
These are expected to increase the risk of systemic side effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic side effects of corticosteroids, and if so, patients should be monitored for systemic adverse events of corticosteroids.

Anticholinergic, neuromuscular blockers:
Corticosteroids may affect the effect of anticholinergics.
1) Acute myopathy has been reported with concomitant use of high doses of corticosteroids and anticholinergics such as neuromuscular blockers (see section 4.4).
2) Antagonism with the neuromuscular blocking effect of pancuronium and vecuronium has been reported in patients taking glucocorticosteroids. This interaction can be expected with all competitive neuromuscular blockers.

Anticholinesterases:
Interaction between glucocorticoids and anticholinesterases such as ambenonium, neostigmine and pyridostigmine may lead to significant potency in myasthenia gravis.

If possible, treatment with anticholinesterase should be discontinued at least 24 hours before administration of glucocorticoid.

4.6 Fertility, pregnancy and lactation

Fertility
Animal studies have shown that corticosteroids impair fertility (see section 5.3).

Pregnancy
In animal studies, corticosteroids have been shown to give rise to various types of malformations (palate gap, skeletal malformations, see section 5.3).

The relevance in humans is unknown.

After long-term treatment, reduced placental and birth weight have been observed in humans and animals.

In addition, there is a risk of adrenal insufficiency in the newborn during long-term treatment. Therefore, during pregnancy, corticosteroids should be given after special consideration.

Breast-feeding
Prednisolone passes into breast milk, but the risk of affecting the baby seems unlikely with therapeutic doses.

4.7 Effects on ability to drive and use machines

The effect of corticosteroids on the ability to drive and use machines has not been systematically investigated.

Side effects such as dizziness, visual disturbances and fatigue are possible after treatment with corticosteroids. In such adverse reactions, patients should not drive or use machines.

4.8 Undesirable effects

The following side effects have been observed and reported during treatment with Prednisolone Pfizer at the following frequencies: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Organ system	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations	Opportunistic infection Activation of infection (e.g., tuberculosis)			
Blood and lymphatic system				Leukocytosis (due to redistribution of intravascular granulocytes)
Immune system disorders				Drug hypersensitivity Anaphylactic
Endocrine disorders	Inhibition of endogenous ACTH and cortisol secretion, Cushing-like symptoms. Growth retardation (in children)			Steroid withdrawal syndrome (see section 4.4) Pheochromocytoma-related crisis (see section 4.4)
Metabolism and nutrition disorders	Hypokalemia Sodium retention Increased gluconeogenesis Catabolic effects Osteoporosis			Metabolic acidosis Fluid retention Hypokalemic alkalosis Dyslipidemia Reduced glucose tolerance (diabetes mellitus

				may deteriorate and latent diabetes become manifest) Lipomatosis Increased appetite (which can lead to weight gain)
Psychiatric disorders		Activation of previous mental disorders (high dose)	Depression, mania in patients without previously known mental illness	Affective disorder (includes euphoria, affective lability, drug-related, suicidal condition) Psychotic disorder (includes delusions, hallucinations and schizophrenia) Mental illness Personality change Confusion state Anxiety Mood swings Abnormal behaviour Insomnia Irritability
Nervous system disorders			Benign intracranial hypertension	Epidural lipomatosis Seizure Amnesia Cognitive disorder Dizziness
Eye disorders		Cataract Glaucoma		Central serous chorioretinopathy (see section 4.4) Exophthalmos Blurred vision (see section 4.4)
Cardiac disorders				Heart failure (in sensitive patients) Bradycardia**
Vascular disorders	Edema hypertension			Thromboembolic events
Respiratory, thoracic and mediastinal disorders				Hiccup

Gastrointestinal disorders				Peptic wound (possibly with perforation and bleeding) Intestinal perforation pancreatitis Ulcerative esophagitis abdominal distension Abdominal pain Diarrhea Dyspepsia Nausea
Skin and subcutaneous tissue disorders	Skin atrophy Impaired wound healing			Angioedema Hirsutism Petechiae Ecchymosis Erythaema hyperhidrosis Stretch marks Itching
Musculoskeletal and connective tissue disorders	Muscular Atrophy		Aseptic bone necrosis Tendon rupture	Muscle weakness Myalgia Myopathy Pathological fracture Neuropathic arthropathy Arthralgia
Renal and urinary disorders				Acute renal crisis (renal crisis in scleroderma) *
Reproductive system and breast disorders				Irregular menstruation
General disorders and administration site conditions				Fatigue Malaise
Investigations				Increased calcium levels in the urine Elevated alanine aminotransferase Elevated aspartate aminotransferase Increased blood alkaline phosphatase

				Elevated blood urea Suppression of skin test reactions[1]

[1] Not MedDRA term.
* Acute renal crisis (scleroderma renal crisis)
The incidence of acute renal crisis varies between the different subpopulations. The greatest risk has been reported in patients with diffuse systemic sclerosis. The minimum risk has been reported in patients with limited systemic sclerosis (2%) and systemic sclerosis with juvenile onset (1%).
** Following high doses.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Reports of acute toxicity and / or death following glucocorticoid overdose are rare.

Possibly, acute overdose may aggravate preexisting disease states such as ulcers, electrolyte disorders, infections and edema.

Treatment: Not usually required. If proper gastric emptying, with charcoal. In case of overdose, there is no specific antidote, but the treatment is supportive and symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoid
ATC code: H02AB06

Synthetic glucocorticoid with anti-inflammatory, immunosuppressive and antiallergic action.

Prednisolone has, by weight, 4-5 times higher anti-inflammatory effect than cortisone, but affects electrolyte turnover to a lesser extent.

The mechanism of action is not yet fully understood.

5.2 Pharmacokinetic properties

Absorption
Prednisolone is rapidly absorbed into the gastrointestinal tract when given orally. Maximum plasma concentration is achieved after 1 to 2 hours after oral administration. The plasma half-life is normally 2 to 4 hours. Its initial absorption, but not total bioavailability, is affected by food.

Distribution
Prednisolone is highly bound to plasma proteins and has high affinity for the transcortin.

The volume of distribution and clearance are reported to increase with transition from low to medium doses.

Metabolism
Prednisolone is metabolised primarily in the liver to a biologically inactive compound.

Prednisolone can be reversibly converted to prednisone by 11β-hydroxysteroid dehydrogenase.

The absolute bioavailability of prednisolone is on average 82% compared to intravenously administered prednisolone following a single 10 mg dose. At normal dosing, the effective duration is calculated to be 12-36 hours.

Elimination
Prednisolone is excreted via the urine as free and conjugated metabolites, along with small amounts of unchanged prednisolone.

More than 90% of the given amount is excreted in the urine. 7-15% is excreted in unchanged form.

5.3 Preclinical safety data

In animal experiments, corticosteroids have been shown to give rise to various types of malformations (palate gap, skeletal malformations). After long-term treatment, reduced placental and birth weight have been observed in animals. Corticosteroids have been shown to reduce fertility when administered to the rat.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Pregelatinised starch

Sodium starch glycolate, type A

Iron oxide yellow (E172)

Iron oxide red (E172)

Glycerol dibehenate

Magnesium stearate

6.2 Incompatibilities

None known

6.3 Shelf life

24 months

6.4 Special precautions for storage

Keep the blister packs in the outer carton in order to protect from light.

6.5 Nature and contents of container

Blisters of AL/PVC containing packs of 28 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not available

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 00142/0843

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/04/2016

10 DATE OF REVISION OF THE TEXT

23/03/2023

Appendix 4 – SmPC for Hydrocortisone 100mg powder for solution for infection/infusion

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hydrocortisone 100mg, powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains Hydrocortisone Sodium Succinate 133.7 mg equivalent to hydrocortisone 100.0 mg

Excipient with known effect:
Each vial contains 6.2 mg (0.3mmol) of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White to almost white powder for parenteral use.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Anti-inflammatory agent.

Hydrocortisone is indicated for any condition in which rapid and intense corticosteroid effect is required such as:

1. *Collagen diseases*
   Systemic lupus erythematosus

2. *Dermatological diseases*
   Severe erythema multiforme (Stevens-Johnson syndrome)

3. *Allergic states*
   Bronchial asthma, anaphylactic reactions

4. *Gastro-intestinal diseases*
   Ulcerative colitis, Crohn's disease

5. *Respiratory diseases*
Aspiration of gastric contents

4.2 Posology and method of administration

Hydrocortisone may be administered by intravenous injection, by intravenous infusion or by intramuscular injection, the preferred method for initial emergency use being intravenous injection. Following the initial emergency period, consideration should be given to employing a longer-acting injectable preparation or an oral preparation.

Dosage usually ranges from 100 mg to 500 mg depending on the severity of the condition, administered by intravenous injection over a period of one to ten minutes. This dose may be repeated at intervals of 2, 4 or 6 hours as indicated by the patient's response and clinical condition.

In general high-dose corticosteroid therapy should be continued only until the patient's condition has stabilised - usually not beyond 48 to 72 hours. If hydrocortisone therapy must be continued beyond 48 to 72 hours hypernatraemia may occur, therefore it may be preferable to replace Hydrocortisone with a corticosteroid such as methylprednisolone sodium succinate as little or no sodium retention occurs.
Although adverse effects associated with high dose, short-term corticoid therapy are uncommon, peptic ulceration may occur. Prophylactic antacid therapy may be indicated.

Patients subjected to severe stress following corticoid therapy should be observed closely for signs and symptoms of adrenocortical insufficiency.

Corticosteroid therapy is an adjunct to, and not a replacement for, conventional therapy.

In patients with liver disease, there may be an increased effect (see section 4.4) and reduced dosing may be considered.

Elderly patients: Hydrocortisone is primarily used in acute short-term conditions. There is no information to suggest that a change in dosage is warranted in the elderly.
However, treatment of elderly patients should be planned bearing in mind the more serious consequences of the common side-effects of corticosteroids in old age and close clinical supervision is required (See Section 4.4).

Paediatric population: While the dose may be reduced for infants and children, it is governed more by the severity of the condition and response of the patient than by age or body weight but should not be less than 25 mg daily (see Special warnings and special precautions for use).

Preparation of solutions: For intravenous or intramuscular injection prepare the solution aseptically by adding not more than 2 ml of sterile water for injections to the contents of one vial of Hydrocortisone 100 mg, shake and withdraw for use.

For intravenous infusion, first prepare the solution by adding not more than 2 ml of sterile water for injections to the vial; this solution may then be added to 100 ml - 1000 ml (but not less than 100 ml) of 5% dextrose in water (or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium

restriction).

When reconstituted as directed the pH of the solution will range from 7.0 to 8.0 and the appearance of the solution is clear and colourless to almost colourless.

4.3 Contraindications

Hydrocortisone is contra-indicated:
- where there is known hypersensitivity to the active substance or any of the excipients listed in section 6.1
- in systemic fungal infection unless specific anti-infective therapy is employed.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

4.4 Special warnings and precautions for use

Warnings and Precautions:

1. A Patient Information Leaflet is provided in the pack by the manufacturer.

2. Undesirable effects may be minimised by using the lowest effective dose for the minimum period. Frequent patient review is required to appropriately titrate the dose against disease activity (see Section 4.2).

3. Adrenal cortical atrophy develops during prolonged therapy and may persist for months after stopping treatment. In patients who have received more than physiological doses of systemic corticosteroids (approximately 30 mg hydrocortisone) for greater than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. 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 30 mg hydrocortisone is reached, dose reduction should be slower to allow the HPA-axis to recover.

   Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to 3 weeks is appropriate if it considered that the disease is unlikely to relapse. Abrupt withdrawal of doses up to 160 mg hydrocortisone for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. 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 if taken for greater than 3 weeks.
   - When a short course has been prescribed within one year of cessation of long-term therapy (months or years).
   - Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
   - Patients receiving doses of systemic corticosteroid greater than 160

mg hydrocortisone.
- Patients repeatedly taking doses in the evening.

4. Patients should carry 'Steroid Treatment' cards which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and the duration of treatment.

5. Corticosteroids may mask some signs of infection, and new infections may appear during their use. Suppression of the inflammatory response and immune function increases the susceptibility to fungal, viral and bacterial infections and their severity. The clinical presentation may often be atypical and may reach an advanced stage before being recognised.

6. Chickenpox is of serious concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunization with varicella/zoster immunoglobin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

7. Exposure to measles should be avoided. Medical advice should be sought immediately if exposure occurs. Prophylaxis with normal intramuscular immuneglobulin may be needed.

8. Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

9 The use of Hydrocortisone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate antituberculosis regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

10. Rarely anaphylactoid reactions have been reported following parenteral Hydrocortisone therapy. Physicians using the drug should be prepared to deal with such a possibility. Appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of drug allergy.

11. Care should be taken for patients receiving cardioactive drugs such as digoxin because of steroid induced electrolyte disturbance/potassium loss (see Section 4.8).

12. Hydrocortisone may have an increased effect in patients with liver

diseases since the metabolism and elimination of hydrocortisone is significantly decreased in these patients.

13. Corticosteroid therapy has been associated with central serious chorioretinopathy, which may lead to retinal detachment.

14. There have been reports of epidural lipomatosis in patients taking corticosteroids, typically with long-term use at high doses.

15. Thrombosis including venous thromboembolism has been reported to occur with corticosteroids. As a result corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.

16. Hypertrophic cardiomyopathy was reported after administration of hydrocortisone to prematurely born infants, therefore appropriate diagnostic evaluation and monitoring of cardiac function and structure should be performed.

Special precautions:

Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary.

1. Osteoporosis (post-menopausal females are particularly at risk).

2. Hypertension or congestive heart failure.

3. Existing or previous history of severe affective disorders (especially previous steroid psychosis).

4. Diabetes mellitus (or a family history of diabetes).

5. History of tuberculosis.

6. Glaucoma (or a family history of glaucoma).

7. Previous corticosteroid-induced myopathy.

8. Liver failure or cirrhosis.

9. Renal insufficiency.

10. Epilepsy.

11. Peptic ulceration.

12. Fresh intestinal anastomoses.

13. Predisposition to thrombophlebitis.

14. Abscess or other pyogenic infections.

15. Ulcerative colitis.

16. Diverticulitis.

17. Myasthenia gravis.

18. Ocular herpes simplex, for fear of corneal perforation.

19. Hypothyroidism.

20. Recent myocardial infarction (myocardial rupture has been reported).

21. Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

22. 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.

23. Hydrocortisone can cause elevation of blood pressure, salt and water retention and increased excretion of potassium. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

24. Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5 Interaction with Other Medicaments and Other Forms of Interaction that can increase the risk of side effects), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover 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. Patients/carers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

    Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

Paediatric population: Corticosteroids cause growth retardation in infancy, childhood and adolescence, which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time. The use of steroids

should be restricted to the most serious indications.

Use in the elderly: The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

Systemic corticosteroids are not indicated for, and therefore should not be used to treat traumatic brain injury or stroke because it is unlikely to be of benefit and may even be harmful. For traumatic brain injury a multicenter study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo. A casual association with methylprednisolone sodium succinate treatment has not been established.

This medicinal product contains 0.3 mmol (6.2 mg) of sodium per vial of 100mg hydrocortisone. This means that sodium content has to be taken into consideration by patients on a controlled sodium diet for dose above 370 mg of hydrocortisone.

4.5 Interaction with other medicinal products and other forms of interaction

1. Convulsions have been reported with concurrent use of corticosteroids and ciclosporin. Since concurrent administration of these agents results in a mutual inhibition of metabolism, it is possible that convulsions and other adverse effects associated with the individual use of either drug may be more apt to occur.

2. Drugs that induce hepatic enzymes, such as rifampicin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone, and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced.

3. Drugs which inhibit the CYP3A4 enzyme, such as cimetidine, erythromycin, ketoconazole, itraconazole, diltiazem and mibefradil, may decrease the rate of metabolism of corticosteroids and hence increase the serum concentration.

4. Steroids may reduce the effects of anticholinesterases in myasthenia gravis. The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by corticosteroids, and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.

5. The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

6. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Salicylates and non- steroidal anti-inflammatory agents should be used cautiously in

conjunction with corticosteroids in hypothrombinaemia.

7. Steroids have been reported to interact with neuromuscular blocking agents such as pancuronium with partial reversal of the neuromuscular block.

4.6 Fertility, pregnancy and lactation

Pregnancy
The ability of corticosteroids to cross the placenta varies between individual drugs, however, hydrocortisone readily crosses the placenta.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine 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 in man, however, when administered for long periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra- uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential, however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

Breast-feeding
Corticosteroids are excreted in breast milk, although no data are available for hydrocortisone. Doses up to 160 mg daily of hydrocortisone are unlikely to cause systemic systemic effects in the infant. Infants of mothers taking higher doses than this may have a degree of adrenal suppression, but the benefits of breastfeeding are likely to outweigh any theoretical risk.

Fertility
Corticosteroids have been shown to impair fertility in animal studies. Adverse effects on fertility in rats with corticosterone were observed in males only and were reversible (see section 5.3). The clinical relevance of this information is uncertain.

4.7 Effects on ability to drive and use machines

The effect of corticosteroids on the ability to drive or use machinery has not been systematically evaluated. Undesirable effects, such as syncope, vertigo, and convulsions are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Since Hydrocortisone is normally employed on a short-term basis it is unlikely that side-effects will occur; however, the possibility of side-effects attributable to corticosteroid therapy should be recognised (see Section 4.4).

Undesirable effects are classified into the following categories, according to system organ class, MedDRA terminology and MedDRA frequencies:

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) and
Not known (frequency cannot be estimated from the available data).

Adverse Reactions table	
System organ Class	**Frequency Not Known (Cannot be estimated from available data)**
Infections and infestations	Infection masked; Opportunistic infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Kaposi's sarcoma (has been reported to occur in patients receiving corticosteroid therapy)
Immune system disorders	Hypersensitivity (including anaphylaxis and anaphylactoid reactions [e.g. bronchospasm, laryngeal oedema, urticaria]); May suppress reactions to skin tests
Blood and lymphatic system disorders	Leucocytosis
Endocrine disorders	Cushingoid; Pituitary-adrenal axis suppression; WITHDRAWAL SYMPTOMS - Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. However, this is more applicable to corticosteroids with an indication where continuous therapy is given (see section 4.4); A 'withdrawal syndrome' may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight
Metabolism and nutrition disorders	Sodium retention; Water retention; Alkalosis hypokalaemic; Glucose tolerance impaired; Increased appetite; Weight increased
Psychiatric disorders	Affective disorders (such as irritable, euphoric,

	depressed and labile mood psychological dependence and suicidal thoughts); Psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia); Behavioural disturbances; Irritability; Anxiety; Sleep disturbances; Cognitive dysfunction including confusion and amnesia
Nervous system disorders	Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri) has been reported, usually after treatment withdrawal of hydrocortisone; Benign intracranial hypertension; Convulsions; Epidural lipomatosis
Eye disorders	Cataract subcapsular; Glaucoma; Exophthalmos; Increased intra-ocular pressure, with possible damage to the optic nerve; Corneal or scleral thinning; Exacerbation of ophthalmic viral or fungal disease; Central serous chorioretinopathy
Cardiac disorders	Cardiac failure congestive (in susceptible patients); Myocardial rupture following a myocardial infarction; Hypertrophic cardiomyopathy in prematurely born infants
Vascular disorders	Hypertension; Thrombosis including Thromboembolism
Respiratory, thoracic and mediastinal disorders	Hiccups; Pulmonary embolism
Gastrointestinal disorders	Peptic ulcer (with possible perforation and haemorrhage); Gastric haemorrhage; Pancreatitis; Abdominal distension; Oesophageal ulceration; Oesophageal candidiasis; Intestinal perforation; Dyspepsia; Nausea
Skin & subcutaneous tissue disorders	Petechiae; Telangiectasia; Ecchymosis; Skin atrophy; Skin striae; Skin hyperpigmentation; Skin hypopigmentation; Hirsutism; Acne; Hyperhidrosis
Musculoskeletal,	Myopathy;

connective tissue and bone disorders	Muscular weakness; Osteonecrosis; Osteoporosis; Pathological fracture; Growth retardation
Reproductive system and breast disorders	Menstruation irregular; Amenorrhoea
General disorders and administration site conditions	Impaired healing; Abscess sterile; Malaise
Investigations	Carbohydrate tolerance decreased; Increased insulin requirement (or oral hypoglycemic agents in diabetics); Blood potassium decreased; Nitrogen balance negative (due to protein catabolism); Urine calcium increased; Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood alkaline phosphatase increased; Weight increased
Injury, poisoning and procedural complications	Spinal compression fracture; Tendon rupture (particularly of the Achilles tendon)

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 Yellow Card Scheme at Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no clinical syndrome of acute overdosage with Hydrocortisone.
Hydrocortisone is dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids
ATC code: H02AB09

Hydrocortisone sodium succinate has the same metabolic and anti-

inflammatory actions as hydrocortisone. It is a glucocorticosteroid. Used in pharmacological doses, its actions supress the clinical manifestations of disease in a wide range of disorders.

5.2 Pharmacokinetic properties

Twelve normal subjects received 100, 200 or 400 mg Hydrocortisone intravenously. Radio-immunoassay results were as follows:-

DOSE (mg)	CMAX (mcg/100 ml)	TMAX (h)	12-HR AUC (mg/100 ml x h)
100	132.3	0.35	418.0
200	231.8	0.25	680.0
400	629.8	0.37	1024.0

In another study, a 1 mg/kg i.m. dose of Hydrocortisone peaked in 30-60 minutes, with a plasma cmax of 80 mg/100 ml.

In analysing hydrocortisone metabolism, a 25 mg IV dose resulted in higher plasma concentrations in females than in males.

5.3 Preclinical safety data

Hydrocortisone was not mutagenic in bacterial assays but induced chromosome aberrations in human lymphocytes in vitro and in mice in vivo. Hydrocortisone did not increase tumour incidences in male and female rats during a limited 2-year carcinogenicity study.

Corticosteroids have been shown to reduce fertility when administered to rats. Adverse effects on fertility in rats with corticosterone were observed in males only and were reversible. Decreased weights and microscopic changes in prostate and seminal vesicles were observed. The numbers of implantations and live fetuses were reduced and these effects were not present following mating at the end of the recovery period.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for injection:
Sodium hydrogen phosphate buffer

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and condtions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C and 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in the original package in order to protect from light

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type III colourless glass vials closed by a grey radiosterilised bromobutyl rubber closure and capped with an aluminium flip cap with blue pastic disk.

Box of 10 vials.

6.6 Special precautions for disposal

Instructions for reconstitution:

Hydrocortisone should be reconstituted by adding not more than 2ml of sterile Water for injections to the contents of one vial. A homogeneous solution will be obtained by shaking gently. The solution of the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. The formulation does not contain a preservative and is for single use only. Once opened, the content of a vial should normally be used immediately (see section 6.3).
For instructions on administration, see section 4.2.

For IV infusion, the following solutions can be used: dextrose 5% in water, isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction.

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

7 MARKETING AUTHORISATION HOLDER

PANPHARMA
Z.I. du Clairay
35133 Luitré
France

8 MARKETING AUTHORISATION NUMBER(S)

PL 44124/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/03/2023

10 DATE OF REVISION OF THE TEXT

31/03/2023

Appendix 5 – SmPC for Tamiflu 75mg hard capsules

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 30 mg hard capsules
Tamiflu 45 mg hard capsules
Tamiflu 75 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tamiflu 30 mg hard capsules
Each hard capsule contains oseltamivir phosphate equivalent to 30 mg of oseltamivir.
For the full list of excipients, see section 6.1.

Tamiflu 45 mg hard capsules
Each hard capsule contains oseltamivir phosphate equivalent to 45 mg of oseltamivir.
For the full list of excipients, see section 6.1.

Tamiflu 75 mg hard capsules
Each hard capsule contains oseltamivir phosphate equivalent to 75 mg of oseltamivir.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tamiflu 30 mg hard capsules
The hard capsule consists of a light yellow opaque body bearing the imprint “ROCHE” and a light yellow opaque cap bearing the imprint “30 mg”. Imprints are blue.

Tamiflu 45 mg hard capsules
The hard capsule consists of a grey opaque body bearing the imprint “ROCHE” and a grey opaque cap bearing the imprint “45 mg”. Imprints are blue.

Tamiflu 75 mg hard capsules
The hard capsule consists of a grey opaque body bearing the imprint “ROCHE” and a light yellow opaque cap bearing the imprint “75 mg”. Imprints are blue.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of influenza
Tamiflu is indicated in adults and children including full term neonates who present with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms.

Prevention of influenza
- Post-exposure prevention in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

- The appropriate use of Tamiflu for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in individuals one year of age or older.

- Tamiflu is indicated for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak (see section 5.2).

Tamiflu is not a substitute for influenza vaccination.

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. Decisions regarding the use of oseltamivir for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses, available information on influenza drug susceptibility patterns for each season and the impact of the disease in different geographical areas and patient populations (see section 5.1).

4.2 Posology and method of administration

Posology

Tamiflu hard capsules and Tamiflu suspension are bioequivalent formulations. 75 mg doses can be administered as either
- one 75 mg capsule or
- one 30 mg capsule plus one 45 mg capsule or
- by administering one 30 mg dose plus one 45 mg dose of suspension.

Commercially manufactured Tamiflu powder for oral suspension (6 mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed.

Adults, and adolescents 13 years and over

Treatment: The recommended oral dose is 75 mg oseltamivir twice daily for 5 days for adolescents (13 to 17 years of age) and adults.

Body Weight	**Recommended dose for 5 days**	**Recommended dose for 10 days*** Immunocompromised Patients
> 40 kg	75 mg twice daily	75 mg twice daily

* The recommended treatment duration in immunocompromised adults and adolescents is 10 days. See *Special Populations, Immunocompromised Patients* for more information.

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Post-exposure prevention: The recommended dose for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for 10 days for adolescents (13 to 17 years of age) and adults.

Body Weight	**Recommended dose for 10 days**	**Recommended dose for 10 days** Immunocompromised Patients
> 40 kg	75 mg once daily	75 mg once daily

Therapy should begin as soon as possible within two days of exposure to an infected individual.

Prevention during an influenza epidemic in the community: The recommended dose for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to 6 weeks (or up to 12 weeks in immunocompromised patients, see sections 4.4, 4.8 and 5.1).

Paediatric population

Children 1 to 12 years of age
Tamiflu 30 mg, 45 mg and 75 mg capsules and oral suspension are available for infants and children 1 year of age or older

Treatment: The following weight-adjusted dosing regimens are recommended for treatment of infants and children 1 year of age or older:

Body Weight	**Recommended dose for 5 days**	**Recommended dose for 10 days*** Immunocompromised Patients
10 kg to 15 kg	30 mg twice daily	30 mg twice daily
> 15 kg to 23 kg	45 mg twice daily	45 mg twice daily
> 23 kg to 40 kg	60 mg twice daily	60 mg twice daily
> 40 kg	75 mg twice daily	75 mg twice daily

*The recommended treatment duration in immunocompromised children (≥1 year old) is 10 days. See Special Populations, Immunocompromised Patients for more information.

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Post-exposure prevention: The recommended post-exposure prevention dose of Tamiflu is:

Body Weight	**Recommended dose for 10 days**	**Recommended dose for 10 days** For Immunocomprmised Patients
10 kg to 15 kg	30 mg once daily	30 mg once daily
> 15 kg to 23 kg	45 mg once daily	45 mg once daily
> 23 kg to 40 kg	60 mg once daily	60 mg once daily
> 40 kg	75 mg once daily	75 mg once daily

Prevention during an influenza epidemic in the community: Prevention during an influenza epidemic has not been studied in children below 12 years of age.

Infants 0 – 12 months of age

Treatment: The recommended treatment dose for infants 0 - 12 months of age is 3 mg/kg twice daily. This is based upon pharmacokinetic and safety data indicating that this dose in infants 0 - 12 months provides plasma concentrations of the pro-drug and active metabolite that are anticipated to be clinically efficacious with a safety profile comparable to that seen in older children and adults (see section 5.2). The following dosing regimen is recommended for treatment of infants 0 - 12 months of age:

Body weight*	**Recommended dose for 5 days**	**Recommended dose for 10 days**** Immunocompromised Patients
3 kg	9 mg twice daily	9 mg twice daily
4 kg	12 mg twice daily	12 mg twice daily
5 kg	15 mg twice daily	15 mg twice daily
6 kg	18 mg twice daily	18 mg twice daily
7 kg	21 mg twice daily	21 mg twice daily
8 kg	24 mg twice daily	24 mg twice daily
9 kg	27 mg twice daily	27 mg twice daily
10 kg	30 mg twice daily	30 mg twice daily

* This table is not intended to contain all possible weights for this population. For all patients under the age of 1 year, 3 mg/kg should be used to determine dose regardless of the weight of the patient.
Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.
** The recommended duration in immunocompromised infants (0-12 months old) is **10 days**. See *Special Populations, Immunocompromised Patients* for more information.

This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Post-exposure prevention: The recommended prophylaxis dose for infants less than 1 year of age during a pandemic influenza outbreak is half of the daily treatment dose. This is based upon clinical data in infants and children 1 year of age or older and adults showing that a prophylaxis dose equivalent to half the daily treatment dose is clinically efficacious for the prevention of influenza. The following age-adjusted dosing prophylaxis regimen is recommended for infants 0 - 12 months of age (see Section 5.2 for exposure simulation):

Age	**Recommended dose for 10 days**	**Recommended dose for 10 days** Immunocompromised Patients
0 - 12 months	3 mg/kg once daily	3 mg/kg once daily

This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Prevention during an influenza epidemic in the community: Prevention during an influenza epidemic has not been studied in children 0-12 months of age.

For instructions on preparing the extemporaneous formulation, see section 6.6.

Special populations

Hepatic impairment
No dose adjustment is required either for treatment or for prevention in patients with hepatic dysfunction. No studies have been carried out in paediatric patients with hepatic disorder.

Renal impairment
Treatment of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment. Recommended doses are detailed in the table below.

Creatinine clearance	**Recommended dose for treatment**
> 60 (ml/min)	75 mg twice daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) twice daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) once daily
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after each haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) single dose

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

Prevention of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment as detailed in the table below.

Creatinine clearance	Recommended dose for prevention
> 60 (ml/min)	75 mg once daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) once daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) every second day
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after every second haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) once weekly

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

There is insufficient clinical data available in infants and children (12 years of age and younger) with renal impairment to be able to make any dosing recommendation.

Elderly
No dose adjustment is required, unless there is evidence of moderate or severe renal impairment.

Immunocompromised patients

Treatment: For treatment of influenza, the recommended duration for immunocompromised patients is 10 days (see sections 4.4, 4.8 and 5.1). No dose adjustment is necessary. Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Seasonal prophylaxis: Longer duration of seasonal prophylaxis up to 12 weeks has been evaluated in immunocompromised patients (see sections 4.4, 4.8 and 5.1).

Method of administration

Oral use.
Patients who are unable to swallow capsules may receive appropriate doses of Tamiflu suspension.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses (see section 5.1).

Tamiflu is not a substitute for influenza vaccination. Use of Tamiflu must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as Tamiflu is administered. Tamiflu should be used for the treatment and prevention of influenza only when reliable epidemiological data indicate that influenza virus is circulating in the community. Susceptibility of circulating influenza virus strains to oseltamivir has been shown to be highly variable (see section 5.1). Therefore, prescribers should take into account the most recent information available on oseltamivir susceptibility patterns of the currently circulating viruses when deciding whether to use Tamiflu.

Severe concomitant condition
No information is available regarding the safety and efficacy of oseltamivir in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalisation.

Immunocompromised patients
The efficacy of oseltamivir in either treatment or prophylaxis of influenza in immunocompromised patients has not been firmly established (see section 5.1).

Cardiac / respiratory disease
Efficacy of oseltamivir in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population (see section 5.1).

Paediatric population
No data allowing a dose recommendation for premature children (< 36 weeks post-conceptual age) are currently available.

Severe renal impairment
Dose adjustment is recommended for both treatment and prevention in adolescents (13 to 17 years of age) and adults with severe renal impairment. There is insufficient clinical data available in infants and children (1 year of age or older) with renal impairment to be able to make any dosing recommendation (see sections 4.2 and 5.2).

Neuropsychiatric events
Neuropsychiatric events have been reported during administration of Tamiflu in patients with influenza, especially in children and adolescents. These events are also experienced by patients with influenza without oseltamivir administration. Patients should be closely monitored for behavioural changes, and the benefits and risks of continuing treatment should be carefully evaluated for each patient (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems (see section 5.2), suggest that clinically significant drug interactions via these mechanisms are unlikely.

Probenecid
No dose adjustment is required when co-administering with probenecid in patients with normal renal function. Co-administration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, results in an approximate 2-fold increase in exposure to the active metabolite of oseltamivir.

Amoxicillin
Oseltamivir has no kinetic interaction with amoxicillin, which is eliminated via the same pathway, suggesting that oseltamivir interaction with this pathway is weak.

Renal elimination
Clinically important drug interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these substances, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. However, care should be taken when prescribing oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

Additional information
No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering oseltamivir with paracetamol, acetylsalicylic acid, cimetidine, antacids (magnesium and aluminium hydroxides and calcium carbonates), rimantadine or warfarin (in subjects stable on warfarin and without influenza).

4.6 Fertility, pregnancy and lactation

Pregnancy
Influenza is associated with adverse pregnancy and foetal outcomes, with a risk of major congenital malformations, including congenital heart defects. A large amount of data on oseltamivir exposure of pregnant women from post-marketing reports and observational studies (more than 1000 exposed outcomes during the first trimester) indicate no malformative nor feto/neonatal toxicity by oseltamivir.

However, in one observational study, while the overall malformation risk was not increased, the results for major congenital heart defects diagnosed within 12 months of birth were not conclusive. In this study, the rate of major congenital heart defects following oseltamivir exposure during the first trimester was 1.76% (7 infants out of 397 pregnancies) compared to 1.01% in unexposed pregnancies from the general population (Odds Ratio 1.75, 95% Confidence Interval 0.51 to 5.98). The clinical significance of this finding is not clear, as the study had limited power. Additionally, this study was too small to reliably assess individual types of major malformations; moreover women exposed to oseltamivir and women unexposed could not be made fully comparable, in particular whether or not they had influenza.

Animal studies do not indicate reproductive toxicity (see section 5.3).

The use of Tamiflu may be considered during pregnancy if necessary and after considering the available safety and benefit information (for data on benefit in pregnant women please refer to section 5.1 “treatment of influenza in pregnant women”), and the pathogenicity of the circulating influenza virus strain.

Breastfeeding
In lactating rats, oseltamivir and the active metabolite are excreted in milk. Very limited information is available on children breast-fed by mothers taking oseltamivir and on excretion of oseltamivir in breast milk. Limited data demonstrated that oseltamivir and the active metabolite were detected in breast milk, however the levels were low, which would result in a subtherapeutic dose to the infant. Considering this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the breastfeeding woman, administration of oseltamivir may be considered, where there are clear potential benefits to breastfeeding mothers.

Fertility
Based on preclinical data, there is no evidence that Tamiflu has an effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Tamiflu has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The overall safety profile of Tamiflu is based on data from 6049 adult/adolescent and 1473 paediatric patients treated with Tamiflu or placebo for influenza, and on data from 3990 adult/adolescent and 253 paediatric patients receiving Tamiflu or placebo/no treatment for the prophylaxis of influenza in clinical trials. In addition, 245 immunocompromised patients (including 7 adolescents and 39 children) received Tamiflu for the treatment of influenza and 475 immunocompromised patients (including 18 children, of these 10 Tamiflu and 8 placebo) received Tamiflu or placebo for the prophylaxis of influenza.

In adults/adolescents, the most commonly reported adverse reactions (ARs) were nausea and vomiting in the treatment studies, and nausea in the prevention studies. The majority of these ARs were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2

days. In children, the most commonly reported adverse reaction was vomiting. In the majority of patients, these ARs did not lead to discontinuation of Tamiflu.

The following serious adverse reactions have been rarely reported since oseltamivir has been marketed: Anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice), angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding and neuropsychiatric disorders.
(Regarding neuropsychiatric disorders, see section 4.4.)

Tabulated list of adverse reactions
The ARs listed in the tables below fall into the following categories: 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*), and very rare (< *1/10,000*). ARs are added to the appropriate category in the tables according to the pooled analysis from clinical studies.

Treatment and prevention of influenza in adults and adolescents:
In adult/adolescent treatment and prevention studies, ARs that occurred the most frequently at the recommended dose (75 mg bid for 5 days for treatment and 75 mg od for up to 6 weeks for prophylaxis) are shown in Table 1.

The safety profile reported in subjects who received the recommended dose of Tamiflu for prophylaxis (75 mg once daily for up to 6 weeks) was qualitatively similar to that seen in the treatment studies, despite a longer duration of dosing in the prophylaxis studies.

Table 1 Adverse reactions in studies investigating Tamiflu for treatment and prevention of influenza in adults and adolescents or through post-marketing surveillance

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
Infections and infestations		Bronchitis, Herpes simplex, Nasopharyngitis, Upper respiratory tract infections, Sinusitis		
Blood and lymphatic system disorders				Thrombocytopenia
Immune system disorders			Hypersensitivity reaction	Anaphylactic reactions, Anaphylactoid reactions
Psychiatric disorders				Agitation, Abnormal behaviour, Anxiety, Confusion, Delusions, Delirium, Hallucination, Nightmares, Self-injury
Nervous system disorders	Headache	Insomnia	Altered level of consciousness, Convulsion	
Eye disorders				Visual disturbance
Cardiac disorders			Cardiac arrhythmia	

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
Respiratory, thoracic and mediastinal disorders		Cough, Sore throat, Rhinorrhea		
Gastrointestinal disorders	Nausea	Vomiting Abdominal pain (incl. upper abdominal pain), Dyspepsia		Gastrointestinal bleedings, Haemorrhagic colitis
Hepatobiliary disorders			Elevated liver enzymes	Fulminant hepatitis, Hepatic failure, Hepatitis
Skin and subcutaneous tissue disorders			Eczema, Dermatitis, Rash, Urticaria	Angioneurotic oedema, Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis
General disorders and administration site conditions		Pain Dizziness (incl. vertigo), Fatigue, Pyrexia, Pain in limb		

Treatment and prevention of influenza in children:

A total of 1473 children (including otherwise healthy children aged 1-12 years old and asthmatic children aged 6-12 years old) participated in clinical studies of oseltamivir given for the treatment of influenza. Of those, 851 children received treatment with oseltamivir suspension. A total of 158 children received the recommended dose of Tamiflu once daily in a post-exposure prophylaxis study in households (n = 99), a 6-week paediatric seasonal prophylaxis study (n = 49) and a 12-week paediatric seasonal prophylaxis study in immunocompromised subjects (n = 10).

Table 2 shows the most frequently reported ARs from paediatric clinical trials.

Table 2 Adverse reactions in studies investigating Tamiflu for treatment and prevention of influenza in children (age/weight-based dosing [30 mg to 75 mg o.d.])

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
Infections and infestations		Otitis media,		
Nervous system disorders		Headache		
Eye disorders:		Conjunctivitis (including red eyes, eye discharge and eye pain)		
Ear and labyrinth disorders:		Earache	Tympanic membrane disorder	
Respiratory, thoracic and mediastinal disorders	Cough, Nasal congestion	Rhinorrhoea		
Gastrointestinal disorders	Vomiting	Abdominal pain (incl. upper abdominal pain), Dyspepsia, Nausea		
Skin and subcutaneous tissue disorders			Dermatitis (including allergic and atopic dermatitis)	

Description of selected adverse reactions

Psychiatric disorders and nervous system disorders
Influenza can be associated with a variety of neurologic and behavioural symptoms which can include events such as hallucinations, delirium, and abnormal behaviour, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.

In patients with influenza who were receiving Tamiflu, there have been postmarketing reports of convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares), in a very few cases resulting in self-injury or fatal outcomes. These events were reported primarily among paediatric and adolescent patients and often had an abrupt onset and rapid resolution. The contribution of Tamiflu to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Tamiflu.

Hepato-biliary disorders
Hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness. These cases include fatal fulminant hepatitis/hepatic failure.

Other special populations

Paediatric population (infants less than one year of age)
In two studies to characterise the pharmacokinetics, pharmacodynamics and safety profile of oseltamivir therapy in 135 influenza infected children less than one year of age, the safety profile was similar among age cohorts with vomiting, diarrohea and diaper rash being the most frequently reported

adverse events (see section 5.2). Insufficient data are available for infants who have a post-conceptual age of less than 36 weeks.

Safety information available on oseltamivir administered for treatment of influenza in infants less than one year of age from prospective and retrospective observational studies (comprising together more than 2,400 infants of that age class), epidemiological databases research and postmarketing reports suggest that the safety profile in infants less than one year of age is similar to the established safety profile of children aged one year and older.

Older people and patients with chronic cardiac and/or respiratory disease
The population included in the influenza treatment studies is comprised of otherwise healthy adults/adolescents and patients "at risk" (patients at higher risk of developing complications associated with influenza, e.g. older people and patients with chronic cardiac or respiratory disease). In general, the safety profile in the patients "at risk" was qualitatively similar to that in otherwise healthy adults/adolescents.

Immunocompromised patients

The treatment of influenza in immunocompromised patients were evaluated in two studies receiving standard dose or high dose regimens (double dose or triple dose) of Tamiflu (see section 5.1). The safety profile of Tamiflu observed in these studies was consistent with that observed in previous clinical trials where Tamiflu was administered for treatment of influenza in non-immunocompromised patients across all age groups (otherwise healthy patients or "at risk" patients [i.e., those with respiratory and/or cardiac co-morbidities]). The most frequent adverse reaction reported in immunocompromised children was vomiting (28%).

In a 12-week prophylaxis study in 475 immunocompromised patients, including 18 children 1 to 12 years of age and older, the safety profile in the 238 patients who received oseltamivir was consistent with that previously observed in Tamiflu prophylaxis clinical studies.

Children with pre-existing bronchial asthma
In general, the adverse reaction profile in children with pre-existing bronchial asthma was qualitatively similar to that of otherwise healthy children.

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

Reports of overdoses with Tamiflu have been received from clinical trials and during post-marketing experience. In the majority of cases reporting overdose, no adverse events were reported.

Adverse events reported following overdose were similar in nature and distribution to those observed with therapeutic doses of Tamiflu, described in section 4.8 Undesirable effects.

No specific antidote is known.

Paediatric population
Overdose has been reported more frequently for children than adults and adolescents. Caution should be exercised when preparing Tamiflu oral suspension and when administering Tamiflu products to children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors ATC code: J05AH02

Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity *in vivo* in animal models of influenza infection at antiviral exposures similar to that achieved in man with 75 mg twice daily.

Antiviral activity of oseltamivir was supported for influenza A and B by experimental challenge studies in healthy volunteers.

Neuraminidase enzyme IC50 values for oseltamivir for clinically isolated influenza A ranged from 0.1 nM to 1.3 nM, and for influenza B was 2.6 nM. Higher IC50 values for influenza B, up to a median of 8.5 nM, have been observed in published studies.

Clinical studies

Treatment of influenza infection

The indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A.

Oseltamivir is effective only against illnesses caused by influenza virus. Statistical analyses are therefore presented only for influenza-infected subjects. In the pooled treatment study population, which included both influenza-positive and -negative subjects (ITT), primary efficacy was reduced proportionally to the number of influenza-negative individuals. In the overall treatment population, influenza infection was confirmed in 67 % (range 46 % to 74 %) of the recruited patients. Of the older subjects, 64 % were influenza-positive and of those with chronic cardiac and/or respiratory disease 62 % were influenza-positive. In all phase III treatment studies, patients were recruited only during the period in which influenza was circulating in the local community.

Adults and adolescents 13 years of age and older: Patients were eligible if they reported within 36 hours of onset of symptoms, had fever ≥ 37.8 °C, accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue or headache). In a pooled analysis of all influenza-positive adults and adolescents (N = 2,413) enrolled into treatment studies, oseltamivir 75 mg twice daily for 5 days reduced the median duration of influenza illness by approximately one day from 5.2 days (95 % CI 4.9 – 5.5 days) in the placebo group to 4.2 days (95 % CI 4.0 – 4.4 days; $p \leq 0.0001$).

The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7 % (135/1,063) in the placebo group to 8.6 % (116/1,350) in the oseltamivir treated population ($p = 0.0012$).

Treatment of influenza in high risk populations: The median duration of influenza illness in older subjects (≥ 65 years) and in subjects with chronic cardiac and/or respiratory disease receiving oseltamivir 75 mg twice daily for 5 days was not reduced significantly. The total duration of fever was reduced by one day in the groups treated with oseltamivir. In influenza-positive older people ,

oseltamivir significantly reduced the incidence of specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics from 19 % (52/268) in the placebo group to 12 % (29/250) in the oseltamivir treated population (p = 0.0156).

In influenza-positive patients with chronic cardiac and/or respiratory disease, the combined incidence of lower respiratory tract complications (mainly bronchitis) treated with antibiotics was 17 % (22/133) in the placebo group and 14 % (16/118) in the oseltamivir treated population (p = 0.5976).

Treatment of influenza in pregnant women: No controlled clinical studies have been conducted on the use of oseltamivir in pregnant women, however, there is evidence from post-marketing and retrospective observational studies showing benefit of the current dosing regimen in this patient population in terms of lower morbidity/mortality. Results from pharmacokinetic analyses indicate a lower exposure to the active metabolite, however dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza (see section 5.2, Pharmacokinetics, Special Population).

Treatment of influenza in children: In a study of otherwise healthy children (65 % influenza-positive) aged 1 to 12 years (mean age 5.3 years) who had fever (≥ 37.8 °C) plus either cough or coryza, 67 % of influenza-positive patients were infected with influenza A and 33 % with influenza B. Oseltamivir treatment, started within 48 hours of onset of symptoms, significantly reduced the time to freedom from illness (defined as the simultaneous return to normal health and activity and alleviation of fever, cough and coryza) by 1.5 days (95 % CI 0.6 – 2.2 days; p < 0.0001) compared to placebo. Oseltamivir reduced the incidence of acute otitis media from 26.5 % (53/200) in the placebo group to 16 % (29/183) in the oseltamivir treated children (p = 0.013).

A second study was completed in 334 asthmatic children aged 6 to 12 years old of which 53.6 % were influenza-positive. In the oseltamivir treated group, the median duration of illness was not reduced significantly. By day 6 (the last day of treatment) FEV_1 had increased by 10.8 % in the oseltamivir treated group compared to 4.7 % on placebo (p = 0.0148) in this population.

The European Medicines Agency has deferred the obligation to submit the results of studies with Tamiflu in one or more subsets of the paediatric population in influenza. See section 4.2 for information on paediatric use.

The indication in infants below the age of 1 is based upon extrapolation of efficacy data from older children and the recommended posology is based upon pharmacokinetic modelling data (see Section 5.2).

Treatment of influenza B infection: Overall, 15 % of the influenza-positive population were infected by influenza B, proportions ranging from 1 to 33 % in individual studies. The median duration of illness in influenza B infected subjects did not differ significantly between the treatment groups in individual studies. Data from 504 influenza B infected subjects were pooled across all studies for analysis. Oseltamivir reduced the time to alleviation of all symptoms by 0.7 days (95 % CI 0.1 – 1.6 days; p = 0.022) and the duration of fever (≥ 37.8 °C), cough and coryza by one day (95 % CI 0.4 – 1.7 days; p < 0.001) compared to placebo.

Treatment of influenza in immunocompromised patients: A randomized, double blind study, to evaluate safety and characterize the effects of oseltamivir on the development of resistant influenza virus (primary analysis) in influenza-infected immunocompromised patients, included 151 adult patients, 7 adolescents and 9 children evaluable for efficacy of oseltamivir (secondary analysis, not powered). The study included solid organ transplant [SOT] patients, haematopoietic stem cell transplant [HSCT] patients, HIV positive patients with a CD4+ cell count <500 cells/mm3, patients on systemic immunosuppressive therapy, and those with haematological malignancy. These patients were randomized to be treated, within 96 hours of symptoms onset for a duration of 10 days. The treatment regimens were: standard dose (75mg or weight adjusted dose for children) twice daily (73 adult patients, 4 adolescent patients and 4 children) or double dose (150 mg or weight-adjusted dose for children) twice daily (78 adult patients, 3 adolescent patients and 5 children) of oseltamivir.

The median time to resolution of symptoms (TTRS) for adults and adolescents was similar between the standard dose group (103.4 hours [95% CI 75.4-122.7]) and double dose group (107.2 hours [95% CI 63.9-140.0]). The TTRS for children was variable and the interpretation is limited by the small sample size. The proportion of adult patients with secondary infections in the standard dose group and double dose group was comparable (8.2% vs 5.1%). For adolescents and children, only one patient (an adolescent) in the standard dose group experienced a secondary infection (bacterial sinusitis).

A pharmacokinetics and pharmacodynamics study was conducted in severely immunocompromised children (≤12 years of age, n=30) receiving standard (75 mg or weight adjusted twice daily) vs. triple dose (225 mg or weight adjusted twice daily) oseltamivir for an adaptive dosing period of 5 to 20 days dependant on duration of viral shedding (mean treatment duration: 9 days). No patients in the standard dose group and 2 patients in the triple dose group reported secondary bacterial infections (bronchitis and sinusitis).

Prevention of influenza
The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households and two seasonal prevention studies. The primary efficacy parameter for all of these studies was the incidence of laboratory-confirmed influenza. The virulence of influenza epidemics is not predictable and varies within a region and from season to season, therefore the number needed to treat (NNT) in order to prevent one case of influenza illness varies.

Post-exposure prevention: In a study in contacts (12.6 % vaccinated against influenza) of an index case of influenza, oseltamivir 75 mg once daily was started within 2 days of onset of symptoms in the index case and continued for seven days. Influenza was confirmed in 163 out of 377 index cases. Oseltamivir significantly reduced the incidence of clinical influenza illness occurring in the contacts of confirmed influenza cases from 24/200 (12 %) in the placebo group to 2/205 (1 %) in the oseltamivir group (92 % reduction [95 % CI 6 – 16; $p \leq 0.0001$]). The number needed to treat (NNT) in contacts of true influenza cases was 10 (95 % CI 9 – 12) and was 16 (95 % CI 15 – 19) in the whole population (ITT) regardless of infection status in the index case.

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, and children aged 1 to 12 years, both as index cases and as family contacts. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza in the households. Oseltamivir prophylaxis lasted for 10 days. In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20 % (27/136) in the group not receiving prevention to 7 % (10/135) in the group receiving prevention (62.7 % reduction [95 % CI 26.0 – 81.2; $p = 0.0042$]). In households of influenza-infected index cases, there was a reduction in the incidence of influenza from 26 % (23/89) in the group not receiving prevention to 11 % (9/84) in the group receiving prevention (58.5 % reduction [95 % CI 15.6 – 79.6; $p = 0.0114$]).
According to subgroup analysis in children at 1 to 12 years of age, the incidence of laboratory-confirmed clinical influenza among children was significantly reduced from 19 % (21/111) in the group not receiving prevention to 7 % (7/104) in the group receiving prevention (64.4 % reduction [95 % CI 15.8 – 85.0; $p = 0.0188$]). Among children who were not already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was reduced from 21 % (15/70) in the group not receiving prevention to 4 % (2/47) in the group receiving prevention (80.1 % reduction [95 % CI 22.0 – 94.9; $p = 0.0206$]). The NNT for the total paediatric population was 9 (95 % CI 7 – 24) and 8 (95 % CI 6, upper limit not estimable) in the whole population (ITT) and in paediatric contacts of infected index cases (ITTII), respectively.

Post-exposure prevention of influenza in infants less than 1 year of age during a pandemic:
Prevention during an influenza pandemic has not been studied in controlled clinical studies in children 0-12 months of age. See Section 5.2 for exposure simulation details.

Prevention during an influenza epidemic in the community: In a pooled analysis of two other studies conducted in unvaccinated otherwise healthy adults, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 25/519 (4.8 %) in the placebo group to 6/520 (1.2 %) in the oseltamivir group (76 % reduction [95 % CI 1.6 – 5.7; p = 0.0006]) during a community outbreak of influenza. The NNT in this study was 28 (95 % CI 24 – 50).
A study in older people in nursing homes, where 80 % of participants received vaccine in the season of the study, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 12/272 (4.4 %) in the placebo group to 1/276 (0.4 %) in the oseltamivir group (92 % reduction [95 % CI 1.5 – 6.6; p = 0.0015]). The NNT in this study was 25 (95 % CI 23 – 62).

Prophylaxis of influenza in immunocompromised patients: A double-blind, placebo-controlled, randomised study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised patients (388 patients with solid organ transplantation [195 placebo; 193 oseltamivir], 87 patients with haemopoetic stem cell transplantation [43 placebo; 44 oseltamivir], no patient with other immunosuppressant conditions), including 18 children 1 to 12 years of age. The primary endpoint in this study was the incidence of laboratory-confirmed clinical influenza as determined by viral culture and/or a four-fold rise in HAI antibodies. The incidence of laboratory-confirmed clinical influenza was 2.9 % (7/238) in the placebo group and 2.1 % (5/237) in the oseltamivir group (95 % CI -2.3 % – 4.1 %; p = 0.772).

Specific studies have not been conducted to assess the reduction in the risk of complications.

Oseltamivir resistance
Clinical studies: The risk of emergence of influenza viruses with reduced susceptibility or frank resistance to oseltamivir has been examined during Roche-sponsored clinical studies. Developing oseltamivir-resistant virus during treatment was more frequent in children than adults, ranging from less than 1% in adults to 18% in infants aged below 1 year. Children who were found to carry oseltamivir-resistant virus in general shed the virus for a prolonged period compared with subjects with susceptible virus. However, treatment-emergent resistance to oseltamivir did not affect treatment response and caused no prolongation of influenza symptoms.

An overall higher incidence of oseltamivir-resistance was observed in adult and adolescent immunocompromised patients treated with standard dose or double dose of oseltamivir for a duration of 10 days [14.5% (10/69) in standard dose group and 2.7% (2/74) in double dose group], compared to data from studies with oseltamivir-treated otherwise healthy adult and adolescent patients. The majority of adult patients that developed resistance were transplant recipients (8/10 patients in the standard dose group and 2/2 patients in the double dose group). Most of the patients with oseltamivir-resistant virus were infected with influenza type A and had prolonged viral shedding.

The incidence of oseltamivir-resistance observed in immunocompromised children (≤12 years of age) treated with Tamiflu across the two studies and evaluated for resistance was 20.7% (6/29). Of the six immunocompromised children found with treatment-emergent resistance to oseltamivir, 3 patients received standard dose and 3 patients high dose (double or triple dose). The majority had acute lymphoid leukemia and were ≤ 5 years of age.

Incidence of Oseltamivir Resistance in Clinical Studies

Patient Population	Patients with Resistance Mutations (%)	
	Phenotyping*	**Geno- and Phenotyping***
Adults and adolescents	0.88% (21/2382)	1.13% (27/2396)
Children (1-12 years)	4.11% (71/1726)	4.52% (78/1727)
Infants (<1year)	18.31% (13/71)	18.31% (13/71)

* Full genotyping was not performed in all studies.

Prophylaxis of Influenza
There has been no evidence for emergence of drug resistance associated with the use of Tamiflu in clinical studies conducted to date in post-exposure (7 days), post-exposure within household groups (10 days) and seasonal (42 days) prevention of influenza in immunocompetent patients. There was no resistance observed during a 12-week prophylaxis study in immunocompromised patients.

Clinical and surveillance data: Natural mutations associated with reduced susceptibility to oseltamivir *in vitro* have been detected in influenza A and B viruses isolated from patients without exposure to oseltamivir. Resistant strains selected during oseltamivir treatment have been isolated from both immunocompetent and immunocompromised patients. Immunocompromised patients and young children are at a higher risk of developing oseltamivir-resistant virus during treatment.

Oseltamivir-resistant viruses isolated from oseltamivir-treated patients and oseltamivir-resistant laboratory strains of influenza viruses have been found to contain mutations in N1 and N2 neuraminidases. Resistance mutations tend to be viral sub-type specific. Since 2007 naturally occurring resistance associated with the H275Y mutation in seasonal H1N1 strains has been sporadically detected. The susceptibility to oseltamivir and the prevalence of such viruses appear to vary seasonally and geographically. In 2008, H275Y was found in > 99 % of circulating H1N1 influenza isolates in Europe. The 2009 H1N1 influenza ("swine flu") was almost uniformly susceptible to oseltamivir, with only sporadic reports of resistance in connection with both therapeutic and prophylactic regimens.

5.2 Pharmacokinetic properties

General Information

Absorption
Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic esterases to the active metabolite (oseltamivir carboxylate). At least 75 % of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5 % relative to the active metabolite. Plasma concentrations of both pro-drug and active metabolite are proportional to dose and are unaffected by co-administration with food.

Distribution
The mean volume of distribution at steady state of the oseltamivir carboxylate is approximately 23 litres in humans, a volume equivalent to extracellular body fluid. Since neuraminidase activity is extracellular, oseltamivir carboxylate distributes to all sites of influenza virus spread.

The binding of the oseltamivir carboxylate to human plasma protein is negligible (approximately 3 %).

Biotransformation
Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. *In vitro* studies demonstrated that neither oseltamivir nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. No phase 2 conjugates of either compound have been identified *in vivo*.

Elimination
Absorbed oseltamivir is primarily (> 90 %) eliminated by conversion to oseltamivir carboxylate. It is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18.8 l/h) exceeds glomerular filtration rate (7.5 l/h) indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20 % of an oral radiolabelled dose is eliminated in faeces.

Other special populations

Paediatric population

Infants less than 1 year of age: The pharmacokinetics, pharmacodynamics and safety of Tamiflu have been evaluated in two uncontrolled open-label studies including influenza infected children less than one year of age (n=135). The rate of clearance of the active metabolite, corrected for body-weight, decreases with ages below one year. Metabolite exposures are also more variable in the youngest infants. The available data indicates that the exposure following a 3 mg/kg dose in infants 0 - 12 months of age provides pro-drug and metabolite exposures anticipated to be efficacious with a safety profile comparable to that seen in older children and adults using the approved dose (see sections 4.1 and 4.2).The reported adverse events were consistent with the established safety profile in older children.

There are no data available for infants below 1 year of age for post exposure prevention of influenza. Prevention during an influenza epidemic in the community has not been studied in children below 12 years of age.

Post-exposure prevention of influenza in infants less than 1 year of age during a pandemic:
Simulation of once daily dosing of 3mg/kg in infants <1 year shows an exposure in the same range or higher than for once daily dosing of 75 mg in adults. Exposure does not exceed that for treatment of infants < 1 year (3 mg/kg twice daily) and is anticipated to result in a comparable safety profile (see Section 4.8). No clinical studies of prophylaxis in infants aged <1 have been performed.

Infants and children 1 year of age or older: The pharmacokinetics of oseltamivir have been evaluated in single-dose pharmacokinetic studies in infants, children and adolescents 1 to 16 years of age. Multiple-dose pharmacokinetics were studied in a small number of children enrolled in a clinical efficacy study. Younger children cleared both the pro-drug and its active metabolite faster than adults, resulting in a lower exposure for a given mg/kg dose. Doses of 2 mg/kg give oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children and adolescents 12 years of age or older are similar to those in adults.

Elderly
Exposure to the active metabolite at steady state was 25 to 35 % higher in older people (age 65 to 78 years) compared to adults less than 65 years of age given comparable doses of oseltamivir. Half-lives observed in older people were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for older people unless there is evidence of moderate or severe renal impairment (creatinine clearance below 60 ml /min) (see section 4.2).

Renal impairment
Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. For dosing, see section 4.2.

Hepatic impairment
In vitro studies have concluded that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment (see section 4.2).

Pregnant Women
A pooled population pharmacokinetic analysis indicates that the Tamiflu dosage regimen described in Section 4.2 Posology and method of administration results in lower exposure (30% on average across all trimesters) to the active metabolite in pregnant women compared to non-pregnant women. The lower predicted exposure however, remains above inhibitoy concentrations (IC95 values) and at a therapeutic level for a range of influenza virus strains. In addition, there is evidence from

observational studies showing benefit of the current dosing regimen in this patient population. Therefore, dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza (see section 4.6 Fertility, pregnancy and lactation).

Immunocompromised Patients
Population pharmacokinetic analyses indicate that treatment of adult and paediatric (<18 years old) immunocompromised patients with oseltamivir (as described in Section 4.2. Posology and method of administration) results in an increased predicted exposure (from approximately 5% up to 50%) to the active metabolite when compared to non-immunocompromised patients with comparable creatinine clearance. Due to the wide safety margin of the active metabolite, no dose adjustments are required in patients due to their immunocompromised status. However, for immunocompromised patients with renal impairment, doses should be adjusted as outlined in section 4.2. Posology and method of administration.

Pharmacokinetic and pharmacodynamic analyses from two studies in immunocompromised patients indicated that there was no meaningful additional benefit in exposures higher than those achieved after the administration of the standard dose.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity. Results of the conventional rodent carcinogenicity studies showed a trend towards a dose-dependent increase in the incidence of some tumours that are typical for the rodent strains used. Considering the margins of exposure in relation to the expected exposure in the human use, these findings do not change the benefit-risk of Tamiflu in its adopted therapeutic indications.

Teratology studies have been conducted in rats and rabbits at doses of up to 1,500 mg/kg/day and 500 mg/kg/day, respectively. No effects on foetal development were observed. A rat fertility study up to a dose of 1,500 mg/kg/day demonstrated no adverse reactions on either sex. In pre- and post-natal rat studies, prolonged parturition was noted at 1,500 mg/kg/day: the safety margin between human exposure and the highest no-effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in the rats and rabbits was approximately 15 to 20 % of that of the mother.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. Limited data indicate that oseltamivir and the active metabolite are excreted in human milk. Extrapolation of the animal data provides estimates of 0.01 mg/day and 0.3 mg/day for the respective compounds.

A potential for skin sensitisation to oseltamivir was observed in a "maximisation" test in guinea pigs. Approximately 50 % of the animals treated with the unformulated active substance showed erythema after challenging the induced animals. Reversible irritancy of rabbits' eyes was detected.

Whereas very high oral single doses of oseltamivir phosphate salt, up to the highest dose tested (1,310 mg/kg), had no adverse reactions in adult rats, such doses resulted in toxicity in juvenile 7-day-old rat pups, including death. These reactions were seen at doses of 657 mg/kg and higher. At 500 mg/kg, no adverse reactions were seen, including upon chronic treatment (500 mg/kg/day administered from 7 to 21 days post partum).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tamiflu 30 mg hard capsules
Capsule core
Pregelatinised starch (derived from maize starch)
Talc
Povidone
Croscarmellose sodium
Sodium stearyl fumarate

Capsule shell
Gelatin
Yellow iron oxide (E172)
Red iron oxide (E172)
Titanium dioxide (E171)

Printing ink
Shellac
Titanium dioxide (E171)
FD and C Blue 2 (indigo carmine, E132)

Tamiflu 45 mg hard capsules
Capsule core
Pregelatinised starch (derived from maize starch)
Talc
Povidone
Croscarmellose sodium
Sodium stearyl fumarate

Capsule shell
Gelatin
Black iron oxide (E172)
Titanium dioxide (E171)

Printing ink
Shellac
Titanium dioxide (E171)
FD and C Blue 2 (indigo carmine, E132)

Tamiflu 75 mg hard capsules
Capsule core
Pregelatinised starch (derived from maize starch)
Talc
Povidone
Croscarmellose sodium
Sodium stearyl fumarate

Capsule shell
Gelatin
Yellow iron oxide (E172)
Red iron oxide (E172)
Black iron oxide (E172)
Titanium dioxide (E171)

Printing ink
Shellac
Titanium dioxide (E171)
FD and C Blue 2 (indigo carmine, E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Tamiflu 30 mg hard capsules
10 years

Tamiflu 45 mg hard capsules
10 years

Tamiflu 75 mg hard capsules
10 years

Storage of the pharmacy compounded suspension
Shelf life of 10 days when stored below 25 °C.

6.4 Special precautions for storage

Do not store above 25 °C.

For storage conditions of the pharmacy compounded suspension, see section 6.3.

6.5 Nature and contents of container

Triplex blister pack (PVC/PE/PVDC, sealed with aluminium foil).
Pack-size 10 capsules.

6.6 Special precautions for disposal and other handling

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

Extemporaneous formulation

When Tamiflu powder for oral suspension is not available
Commercially manufactured Tamiflu for oral suspension (6 mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed. In the event that commercially manufactured Tamiflu powder for oral suspension is not available, the pharmacist may compound a suspension (6 mg/ml) from Tamiflu capsules or patients can prepare the suspension from capsules at home.

The pharmacy preparation should be preferred to home preparation. Detailed information on the home preparation can be found in the package leaflet of Tamiflu capsules under “Making liquid Tamiflu at home”.

Syringes of appropriate volume and grading should be provided for administering the pharmacy compounded suspension as well as for the procedures involved in the home preparation. In both cases, the correct volumes should preferably be marked on the syringes.

Pharmacy compounding

Pharmacy compounded 6 mg/ml suspension prepared from capsules

Adults, adolescents and infants and children 1 year of age or older who are unable to swallow intact capsules

This procedure describes the preparation of a 6 mg/ml suspension that will provide one patient with enough medicine for a 5-day course of treatment or a 10-day course of prophylaxis. For immunocompromised patients, a 10-day course of treatment is needed.

The pharmacist may compound a 6 mg/ml suspension from Tamiflu 30 mg, 45 mg or 75 mg capsules using water containing 0.05 % w/v sodium benzoate added as a preservative.

First, calculate the total volume needed to be compounded and dispensed to provide a 5-day course of treatment or a 10-day course of prophylaxis for the patient. The total volume required is determined by the weight of the patient according to the recommendation in the table below. To allow for accurate volume withdrawal of up to 10 doses (2 withdrawals per daily treatment dose for 5 days), the column indicating measurement loss is to be considered for compounding.

For immunocompromised patients, calculate the total volume needed to be compounded and dispensed to provide a 10-day course of treatment for the patient. The total volume needed is indicated in the table below for immunocompromised patients and is determined by the patient's weight. To allow for accurate volume withdrawal of up to 20 doses (2 withdrawals per daily treatment dose for 10 days), the column indicating measurement loss is to be considered for compounding.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient's weight for 5-day treatmentor 10-day prophylaxis course

Body weight (kg)	**Total volume to compound per patient weight (ml) Measurement loss not considered**	**Total volume to compound per patient weight (ml) Measurement loss considered**
10 kg to 15 kg	50 ml	60 ml or 75 ml*
> 15 kg to 23 kg	75 ml	90 ml or 100 ml*
> 23 kg to 40 kg	100 ml	125 ml
> 40 kg	125 ml	137.5 ml (or 150 ml)*

* Depending on the capsule strength used.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient's weight for 10-days of treatment for immunocompromised patients

Body weight (kg)	Total volume to compound per patient weight (ml) Measurement loss not considered	Total volume to compound per patient weight (ml) Measurement loss considered
10 kg to 15 kg	100 ml	125 ml
> 15 kg to 23 kg	150 ml	187.5 ml
> 23 kg to 40 kg	200 ml	250 ml
> 40 kg	250 ml	300 ml

Second, determine the number of capsules and the amount of vehicle (water containing 0.05 % w/v sodium benzoate added as a preservative) that is needed to prepare the total volume (calculated from the table above) of pharmacy compounded 6 mg/ml suspension as shown in the table below:

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension (for 5 days of treatment or 10-days of prophylaxis)

Total volume of compounded suspension to be prepared	Required number of Tamiflu capsules (mg of oseltamivir)			Required volume of vehicle
	75 mg	45 mg	30 mg	
60 ml	Please use alternative capsule strength*	8 capsules (360 mg)	12 capsules (360 mg)	59.5 ml
75 ml	6 capsules (450 mg)	10 capsules (450 mg)	15 capsules (450 mg)	74 ml
90 ml	Please use alternative capsule strength*	12 capsules (540 mg)	18 capsules (540 mg)	89 ml
100 ml	8 capsules (600 mg)	Please use alternative capsule strength*	20 capsules (600 mg)	98.5 ml
125 ml	10 capsules (750 mg)	Please use alternative capsule strength*	25 capsules (750 mg)	123.5 ml
137.5 ml	11 capsules (825 mg)	Please use alternative capsule strength*	Please use alternative capsule strength*	136 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension (for 10 days of treatment in immunocompromised patients)

Total volume of compounded suspension to be prepared	Required number of Tamiflu capsules (mg of oseltamivir)			Required volume of vehicle
	75 mg	45 mg	30 mg	
125ml	10 capsules (750 mg)	Please use alternative capsule strength*	25 capsules (750 mg)	123.5 ml
187.5ml	15 capsules (1120 mg)	25 capsules (1120 mg)	Please use alternative capsule strength*	185 ml
250ml	20 capsules (1500 mg)	Please use alternative capsule strength*	50 capsules (1500 mg)	246.5 ml
300ml	24 capsules (1800 mg)	40 capsules (1800 mg)	60 capsules (1800 mg)	296 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.

Third, follow the procedure below for compounding the 6 mg/ml suspension from Tamiflu capsules:

1. In a glass beaker of suitable size place the stated amount of water containing 0.05 % w/v sodium benzoate added as a preservative.
2. Open the stated amount of Tamiflu capsules and transfer the content of each capsule directly to the preserved water in the glass beaker.
3. With a suitable stirring device, stir for 2 minutes.
   (Note: The drug substance, oseltamivir phosphate, readily dissolves in water. The suspension is caused by some of the excipients of Tamiflu capsules, which are insoluble.)
4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5. Close the bottle using a child-resistant cap.
6. Put an ancillary label on the bottle indicating “Shake Gently Before Use”.
   (Note: This compounded suspension should be gently shaken prior to administration to minimise the tendency for air entrapment.)
7. Instruct the parent or caregiver that any remaining material following completion of therapy must be discarded. It is recommended that this information be provided by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
8. Place an appropriate expiration date label according to storage condition (see section 6.3).

Place a pharmacy label on the bottle that includes the patient’s name, dosing instructions, use by date, name of medicinal product and any other required information to be in compliance with local pharmacy regulations. Refer to the table below for the proper dosing instructions.

Dosing chart for pharmacy-compounded 6 mg/ml suspension prepared from Tamiflu capsules for patients 1 year of age or older

Body weight (kg)	**Dose (mg)**	**Volume per dose 6 mg/ml**	**Treatment dose (for 5 days)**	**Treatment dose (for 10 days*)** Immunocompromised patients	**Prophylaxis dose (for 10 days)**
10 kg to 15 kg	30 mg	5 ml	5 ml twice daily	5 ml twice daily	5 ml once daily
> 15 kg to 23 kg	45 mg	7.5 ml	7.5 ml twice daily	7.5 ml twice daily	7.5 ml once daily
> 23 kg to 40 kg	60 mg	10 ml	10 ml twice daily	10 ml twice daily	10 ml once daily
> 40 kg	75 mg	12.5 ml	12.5 ml twice daily	12.5 ml twice daily	12.5 ml once daily

*The recommended duration in immunocompromised patients (≥1 year of age) is **10 days**. See *Special Populations, Immunocompromised Patients for more information.*

Dispense the pharmacy compounded suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (according to the dosing table above) on the oral syringe for each patient.

The appropriate dose must be mixed by the caregiver with an equal quantity of sweet liquid food, such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce) to mask the bitter taste.

Infants less than 1 year of age
This procedure describes the preparation of a 6 mg/ml suspension that will provide one patient with enough medication for a 5-day course of treatment or a 10-day course of prophylaxis. For immunocompromised patients, a 10-day course of treatment for the patient is needed.

The pharmacist may compound a 6 mg/ml suspension from Tamiflu 30 mg, 45 mg or 75 mg capsules using water containing 0.05 % w/v sodium benzoate added as a preservative.

First, calculate the total volume needed to be compounded and dispensed for each patient. The total volume required is determined by the weight of the patient according to the recommendation in the table below. To allow for accurate volume withdrawal of up to 10 doses (2 withdrawals per daily treatment dose for 5 days), the column indicating measurement loss is to be considered for compounding.

For immunocompromised patients, calculate the total volume needed to be compounded and dispensed to provide a 10-day course of treatment for the patient. The total volume needed is indicated in the table below and is determined by the patient's weight. To allow for accurate volume withdrawal of up to 20 doses (2 withdrawals per daily treatment dose for 10 days), the column indicating measurement loss is to be considered for compounding.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient's weight (for 5 days of treatment or 10-days of prophylaxis)

Body weight (kg)	**Total volume to compound per patient weight (ml) Measurement loss not considered**	**Total volume to compound per patient weight (ml) Measurement loss considered**
≤ 7 kg	up to 40 ml	50 ml
> 7 kg to 10 kg	50 ml	60 ml or 75 ml*

* Depending on the capsule strength used.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient's weight (for 10-days of treatment in immunocompromised patients)

Body weight (kg)	Total volume to compound per patient weight (ml) Measurement loss not considered	Total volume to compound per patient weight (ml) Measurement loss considered
≤ 7 kg	up to 80 ml	100 ml
> 7 kg to 10 kg	100 ml	125 ml

Second, determine the number of capsules and the amount of vehicle (water containing 0.05 % w/v sodium benzoate added as a preservative) that is needed to prepare the total volume (calculated from the table above) of pharmacy compounded 6 mg/ml suspension as shown in the table below:

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension (for 5 days of treatment or 10-days of prophylaxis)

Total volume of compounded suspension to be prepared	Required number of Tamiflu capsules (mg of oseltamivir)			Required volume of vehicle
	75 mg	45 mg	30 mg	
50 ml	4 capsules (300 mg)	Please use alternative capsule strength*	10 capsules (300 mg)	49.5 ml
60 ml	Please use alternative capsule strength*	8 capsules (360 mg)	12 capsules (360 mg)	59.5 ml
75 ml	6 capsules (450 mg)	10 capsules (450 mg)	15 capsules (450 mg)	74 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension (for 10-days of treatment in immunocompromised patients)

Total volume of compounded suspension to be prepared	Required number of Tamiflu capsules (mg of oseltamivir)			Required volume of vehicle
	75 mg	45 mg	30 mg	
100 ml	8 capsules (600 mg)	Please use alternative capsule strength*	20 capsules (600 mg)	98.5 ml
125 ml	10 capsules (750 mg)	Please use alternative capsule strength*	25 capsules (750 mg)	123.5 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.

Third, follow the procedure below for compounding the 6 mg/ml suspension from Tamiflu capsules:

1. In a glass beaker of suitable size place the stated amount of water containing 0.05 % w/v sodium benzoate added as a preservative.
2. Open the stated amount of Tamiflu capsules and transfer the content of each capsule directly to the preserved water in the glass beaker.
3. With a suitable stirring device, stir for 2 minutes.
   (Note: The drug substance, oseltamivir phosphate, readily dissolves in water. The suspension is caused by some of the excipients of Tamiflu capsules, which are insoluble.)
4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5. Close the bottle using a child-resistant cap.
6. Put an ancillary label on the bottle indicating "Shake Gently Before Use".
   (Note: This compounded suspension should be gently shaken prior to administration to minimise the tendency for air entrapment.)
7. Instruct the parent or caregiver that any remaining material following completion of therapy must be discarded. It is recommended that this information be provided by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
8. Place an appropriate expiration date label according to storage condition (see section 6.3).

Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, use by date, name of medicinal product and any other required information to be in compliance with local pharmacy regulations. Refer to the table below for the proper dosing instructions.

Dosing chart for pharmacy compounded 6 mg/ml suspension prepared from Tamiflu capsules for infants less than 1 year of age

Body Weight (rounded to the nearest 0.5 kg)	**Dose (mg)**	**Volume per dose (6 mg/ml)**	**Treatment Dose (for 5 days)**	**Treatment Dose (for 10 days*)** Immunocompromised patients	**Prophylaxis Dose (for 10 days)**	**Dispenser size to use (grading 0.1 ml)**
3 kg	9 mg	1.5 ml	1.5 ml twice daily	1.5 ml twice daily	1.5 ml once daily	2.0 ml or 3.0 ml
3.5 kg	10.5 mg	1.8 ml	1.8 ml twice daily	1.8 ml twice daily	1.8 ml once daily	2.0 ml or 3.0 ml
4 kg	12 mg	2.0 ml	2.0 ml twice daily	2.0 ml twice daily	2.0 ml once daily	3.0 ml
4.5 kg	13.5 mg	2.3 ml	2.3 ml twice daily	2.3 ml twice daily	2.3 ml once daily	3.0 ml
5 kg	15 mg	2.5 ml	2.5 ml twice daily	2.5 ml twice daily	2.5 ml once daily	3.0 ml
5.5 kg	16.5 mg	2.8 ml	2.8 ml twice daily	2.8 ml twice daily	2.8 ml once daily	3.0 ml
6 kg	18 mg	3.0 ml	3.0 ml twice daily	3.0 ml twice daily	3.0 ml once daily	3.0 ml (or 5.0 ml)
6.5 kg	19.5 mg	3.3 ml	3.3 ml twice daily	3.3 ml twice daily	3.3 ml once daily	5.0 ml
7 kg	21 mg	3.5 ml	3.5ml twice daily	3.5ml twice daily	3.5 ml once daily	5.0 ml
7.5 kg	22.5 mg	3.8 ml	3.8 ml twice daily	3.8 ml twice daily	3.8 ml once daily	5.0 ml
8 kg	24 mg	4.0 ml	4.0 ml twice daily	4.0 ml twice daily	4.0 ml once daily	5.0 ml
8.5 kg	25.5 mg	4.3 ml	4.3 ml twice daily	4.3 ml twice daily	4.3 ml once daily	5.0 ml
9 kg	27 mg	4.5 ml	4.5 ml twice daily	4.5 ml twice daily	4.5 ml once daily	5.0 ml
9.5 kg	28.5 mg	4.8 ml	4.8 ml twice daily	4.8 ml twice daily	4.8 ml once daily	5.0 ml
10 kg	30 mg	5.0 ml	5.0 ml twice daily	5.0 ml twice daily	5.0 ml once daily	5.0 ml

* The recommended duration in immunocompromised infants (0-12 months old) is **10 days**. See *Special Populations, Immunocompromised Patients* for more information.

Dispense the pharmacy compounded suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (according to the dosing tables above) on the oral syringe for each patient.

The appropriate dose must be mixed by the caregiver with an equal quantity of sweet liquid food, such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce) to mask the bitter taste.

Home preparation

When commercially manufactured Tamiflu oral suspension is not available, a pharmacy compounded suspension prepared from Tamiflu capsules must be used (see detailed instructions above). If the commercially manufactured Tamiflu oral suspension and the pharmacy compounded suspension is also not available, Tamiflu suspension may be prepared at home.

When appropriate capsule strengths are available for the dose needed, the dose is given by opening the capsule and mixing its contents with no more than one teaspoon of a suitable sweetened food product. The bitter taste can be masked by products such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce). The mixture should be stirred and given entirely to the patient. The mixture must be swallowed immediately after its preparation.

When only 75 mg capsules are available, and doses of 30 mg or 45 mg are needed, the preparation of Tamiflu suspension involves additional steps. Detailed instructions can be found in the package leaflet of Tamiflu capsules under “Making liquid Tamiflu at home”.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

Tamiflu 30 mg hard capsules
EU/1/02/222/003

Tamiflu 45 mg hard capsules
EU/1/02/222/004

Tamiflu 75 mg hard capsules
EU/1/02/222/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2002
Date of last renewal: 22 May 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 6 mg/ml powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of reconstituted suspension contains oseltamivir phosphate equivalent to 6 mg of oseltamivir.
One bottle of reconstituted suspension (65 ml) contains 390 mg of oseltamivir.

Excipients with known effect:
5 ml oseltamivir suspension delivers 0.9 g of sorbitol and 2.5 mg of sodium benzoate.
7.5 ml oseltamivir suspension delivers 1.3 g of sorbitol and 3.75 mg of sodium benzoate.
10 ml oseltamivir suspension delivers 1.7 g of sorbitol and 5.0 mg of sodium benzoate.
12.5 ml oseltamivir suspension delivers 2.1 g of sorbitol and 6.25 mg of sodium benzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension
The powder is a granulate or clumped granulate with a white to light yellow colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of influenza
Tamiflu is indicated in adults and children including full term neonates who present with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms.

Prevention of influenza
- Post-exposure prevention in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

- The appropriate use of Tamiflu for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in individuals one year of age or older.

- Tamiflu is indicated for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak (see section 5.2).

Tamiflu is not a substitute for influenza vaccination.

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. Decisions regarding the use of oseltamivir for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses, available information on influenza drug susceptibility patterns for each season and the impact of the disease in different geographical areas and patient populations (see section 5.1).

4.2 Posology and method of administration

Posology

Tamiflu suspension and Tamiflu hard capsules are bioequivalent formulations. 75 mg doses can be administered as either

- one 75 mg capsule or
- one 30 mg capsule plus one 45 mg capsule or
- by administering one 30 mg dose plus one 45 mg dose of suspension.

Adults, adolescents or children (> 40 kg) who are able to swallow capsules may receive appropriate doses of Tamiflu capsules.

Treatment
Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

For adolescents (13 to 17 years of age) and adults: The recommended oral dose is 75 mg oseltamivir twice daily for 5 days (or 10 days in immunocompromised patients).

Paediatric population

For infants and children1 year of age or older: The recommended dose of Tamiflu 6 mg/ml oral suspension is indicated in the table below. Tamiflu 30 mg and 45 mg capsules are available as an alternative to the recommended dose of Tamiflu 6 mg/ml suspension.

The following weight-adjusted dosing regimens are recommended for infants and children 1 year of age or older:

Body weight	**Recommended dose for 5 days**	**Recommended dose for 10 days*** Immunocompromised Patients	**Amount of oral suspension to withdraw**
10 kg to 15 kg	30 mg twice daily	30 mg twice daily	5 ml twice daily
> 15 kg to 23 kg	45 mg twice daily	45 mg twice daily	7.5 ml twice daily
> 23 kg to 40 kg	60 mg twice daily	60 mg twice daily	10 ml twice daily
> 40 kg	75 mg twice daily	75 mg twice daily	12.5 ml twice daily

*The recommended duration in immunocompromised patients (≥1 year old) is **10 days**. See *Special Populations, Immunocompromised Patients* for more information.

Children weighing > 40 kg and who are able to swallow capsules may receive treatment with the adult dosage of 75 mg capsules twice daily for 5 days as an alternative to the recommended dose of Tamiflu suspension.

For infants less than 1 year of age: The recommended treatment dose for infants 0 - 12 months of age is 3 mg/kg twice daily. This is based upon pharmacokinetic and safety data indicating that this dose in infants 0 - 12 months provides plasma concentrations of the pro-drug and active metabolite that are anticipated to be clinically efficacious with a safety profile comparable to that seen in older children and adults (see section 5.2).

A 3 ml oral dispenser (graduated in 0.1 ml steps) should be used for dosing children 0 - 12 months of age requiring 1 ml to 3 ml of Tamiflu 6 mg/ml oral suspension. For higher doses the 10 ml syringe should be used. The following dosing regimen is recommended for treatment of infants below 1 year of age:

Dosing table of oseltamivir for children <u>less than 1 year of age</u> : 3 mg/kg twice daily

Body Weight*	**Recommended dose for 5 days**	**Recommended dose for 10 days**** Immunocompromised patients	**Amount of oral suspension to withdraw**	**Dispenser size to use**
3 kg	9 mg twice daily	9 mg twice daily	1.5 ml twice daily	3 ml
3.5 kg	10.5 mg twice daily	10.5 mg twice daily	1.8 ml twice daily	3 ml
4 kg	12 mg twice daily	12 mg twice daily	2.0 ml twice daily	3 ml
4.5 kg	13.5 mg twice daily	13.5 mg twice daily	2.3 ml twice daily	3 ml
5 kg	15 mg twice daily	15 mg twice daily	2.5 ml twice daily	3 ml
5.5 kg	16.5 mg twice daily	16.5 mg twice daily	2.8 ml twice daily	3 ml
6 kg	18 mg twice daily	18 mg twice daily	3.0 ml twice daily	3 ml
> 6 - 7 kg	21 mg twice daily	21 mg twice daily	3.5 ml twice daily	10 ml
> 7 - 8 kg	24 mg twice daily	24 mg twice daily	4.0 ml twice daily	10 ml
> 8 - 9 kg	27 mg twice daily	27 mg twice daily	4.5 ml twice daily	10 ml
> 9 - 10 kg	30 mg twice daily	30 mg twice daily	5.0 ml twice daily	10 ml

* This table is not intended to contain all possible weights for this population.
The recommended duration in immunocompromised infants (0-12 months old) is **10 days. See *Special Populations, Immunocompromised Patients* for more information.

This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Prevention
<u>Post-exposure prevention</u>
<u>For adolescents (13 to 17 years of age) and adults</u>: The recommended dose for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for 10 days. Therapy should begin as soon as possible within two days of exposure to an infected individual.

<u>For infants and children 1 year of age or older</u>: Tamiflu 30 mg and 45 mg capsules are available as an alternative to the recommended dose of Tamiflu 6 mg/ml suspension.

The recommended post-exposure prevention dose of Tamiflu is:

Body weight	**Recommended dose for 10 days**	**Immunocompromised Patients** Recommended dose for 10 days	**Amount of oral suspension to withdraw**
10 kg to 15 kg	30 mg once daily	30 mg once daily	5 ml once daily
> 15 kg to 23 kg	45 mg once daily	45 mg once daily	7.5 ml once daily
> 23 kg to 40 kg	60 mg once daily	60 mg once daily	10 ml once daily
> 40 kg	75 mg once daily	75 mg once daily	12.5 ml once daily

Children weighing > 40 kg and who are able to swallow capsules may receive prophylaxis with a 75 mg capsule once daily for 10 days as an alternative to the recommended dose of Tamiflu suspension.

<u>For infants less than 1 year of age</u>: The recommended prophylaxis dose for infants less than 12 months during a pandemic influenza outbreak is half of the daily treatment dose. This is based upon clinical

data in children > 1 year of age and adults showing that a prophylaxis dose equivalent to half the daily treatment dose is clinically efficacious for the prevention of influenza (see Section 5.2 for exposure simulation).

In case of a pandemic, a 3 ml oral dispenser (graduated in 0.1 ml steps) should be used for dosing children below 1 year of age requiring 1 ml to 3 ml of Tamiflu 6 mg/ml oral suspension. For higher doses the 10 ml syringe should be used.

The following dosing regimen is recommended for infants less than 1 year of age:

Dosing table of oseltamivir for children below one year of age: 3 mg/kg once daily

Body Weight*	**Recommended dose for 10 days**	**Immunocompromised Patients** Recommended dose for 10 days	**Amount of oral suspension to withdraw**	**Dispenser size to use**
3 kg	9 mg once daily	9 mg once daily	1.5 ml once daily	3 ml
3.5 kg	10.5 mg once daily	10.5 mg once daily	1.8 ml once daily	3 ml
4 kg	12 mg once daily	12 mg once daily	2.0 ml once daily	3 ml
4.5 kg	13.5 mg once daily	13.5 mg once daily	2.3 ml once daily	3 ml
5 kg	15 mg once daily	15 mg once daily	2.5 ml once daily	3 ml
5.5 kg	16.5 mg once daily	16.5 mg once daily	2.8 ml once daily	3 ml
6 kg	18 mg once daily	18 mg once daily	3.0 ml once daily	3 ml
> 6 - 7 kg	21 mg once daily	21 mg once daily	3.5 ml once daily	10 ml
> 7 - 8 kg	24 mg once daily	24 mg once daily	4.0 ml once daily	10 ml
> 8 - 9 kg	27 mg once daily	27 mg once daily	4.5 ml once daily	10 ml
> 9 - 10 kg	30 mg once daily	30 mg once daily	5.0 ml once daily	10 ml

* This table is not intended to contain all possible weights for this population.

This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Prevention during an influenza epidemic in the community
Prevention during an influenza epidemic has not been studied in children below 12 years of age. The recommended dose for adults and adolescents for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to 6 weeks (or up to 12 weeks in immunocompromised patients).

Special populations

Hepatic impairment
No dose adjustment is required either for treatment or for prevention in patients with hepatic dysfunction. No studies have been carried out in paediatric patients with hepatic disorder.

Renal impairment
Treatment of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment. Recommended doses are detailed in the table below.

Creatinine clearance	Recommended dose for treatment
> 60 (ml/min)	75 mg twice daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) twice daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) once daily
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after each haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) single dose

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

Prevention of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment as detailed in the table below.

Creatinine clearance	Recommended dose for prevention
> 60 (ml/min)	75 mg once daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) once daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) every second day
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after every second haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) once weekly

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

There is insufficient clinical data available in infants and children (12 years of age and younger) with renal impairment to be able to make any dosing recommendation.

Elderly
No dose adjustment is required, unless there is evidence of moderate or severe renal impairment.

Immunocompromised patients
Treatment: For treatment of influenza, the recommended duration for immunocompromised patients is 10 days (see sections 4.4, 4.8, 5.1). No dose adjustment is necessary. Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Seasonal prophylaxis: Longer duration of seasonal prophylaxis up to 12 weeks has been evaluated in immunocompromised patients (see sections 4.4, 4.8 and 5.1).

Method of administration
For dosing, a 3 ml and 10 ml oral dispenser is provided in the box.
It is recommended that Tamiflu powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient (see section 6.6).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses (see section 5.1).

Tamiflu is not a substitute for influenza vaccination. Use of Tamiflu must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as Tamiflu is administered. Tamiflu should be used for the treatment and prevention of influenza only when reliable epidemiological data indicate that influenza virus is circulating in the community. Susceptibility of circulating influenza virus strains to oseltamivir has been shown to be highly variable (see section 5.1). Therefore, prescribers should take into account the most recent information available on oseltamivir susceptibility patterns of the currently circulating viruses when deciding whether to use Tamiflu.

Severe concomitant condition
No information is available regarding the safety and efficacy of oseltamivir in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalisation.

Immunocompromised patients
The efficacy of oseltamivir in either treatment or prophylaxis of influenza in immunocompromised patients has not been firmly established(see section 5.1).

Cardiac / respiratory disease
Efficacy of oseltamivir in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population (see section 5.1).

Paediatric population
No data allowing a dose recommendation for premature children (<36 weeks post-conceptual age) are currently available.

Severe renal impairment
Dose adjustment is recommended for both treatment and prevention in adolescents (13 to 17 years of age) and adults with severe renal impairment. There is insufficient clinical data available in infants and children (1 year of age or older) with renal impairment to be able to make any dosing recommendation (see sections 4.2 and 5.2).

Neuropsychiatric events
Neuropsychiatric events have been reported during administration of Tamiflu in patients with influenza, especially in children and adolescents. These events are also experienced by patients with influenza without oseltamivir administration. Patients should be closely monitored for behavioural changes, and the benefits and risks of continuing treatment should be carefully evaluated for each patient (see section 4.8).

Excipients
This medicinal product contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.
Sorbitol may cause gastrointestinal discomfort and mild laxative effect.
This medicinal product contains sodium benzoate. Sodium benzoate (E211) may increase jaundice in newborn babies (up to 4 weeks old).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems (see section 5.2), suggest that clinically significant drug interactions via these mechanisms are unlikely.

Probenecid
No dose adjustment is required when co-administering with probenecid in patients with normal renal function. Co-administration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, results in an approximate 2-fold increase in exposure to the active metabolite of oseltamivir.

Amoxicillin
Oseltamivir has no kinetic interaction with amoxicillin, which is eliminated via the same pathway, suggesting that oseltamivir interaction with this pathway is weak.

Renal elimination
Clinically important drug interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these substances, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. However, care should be taken when prescribing oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

Additional information
No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering oseltamivir with paracetamol, acetylsalicylic acid, cimetidine, antacids (magnesium and aluminium hydroxides and calcium carbonates), rimantadine or warfarin (in subjects stable on warfarin and without influenza).

4.6 Fertility, pregnancy and lactation

Pregnancy
Influenza is associated with adverse pregnancy and foetal outcomes, with a risk of major congenital malformations, including congenital heart defects. A large amount of data on oseltamivir exposure of pregnant women from post-marketing reports and observational studies (more than 1000 exposed outcomes during the first trimester) indicate no malformative nor feto/neonatal toxicity by oseltamivir.

However, in one observational study, while the overall malformation risk was not increased, the results for major congenital heart defects diagnosed within 12 months of birth were not conclusive. In this study, the rate of major congenital heart defects following oseltamivir exposure during the first trimester was 1.76% (7 infants out of 397 pregnancies) compared to 1.01% in unexposed pregnancies from the general population (Odds Ratio 1.75, 95% Confidence Interval 0.51 to 5.98). The clinical significance of this finding is not clear, as the study had limited power. Additionally, this study was too small to reliably assess individual types of major malformations; moreover women exposed to oseltamivir and women unexposed could not be made fully comparable, in particular whether or not they had influenza.

Animal studies do not indicate reproductive toxicity (see section 5.3).

The use of Tamiflu may be considered during pregnancy if necessary and after considering the available safety and benefit information (for data on benefit in pregnant women please refer to section 5.1 “Treatment of influenza in pregnant women”), and the pathogenicity of the circulating influenza virus strain.

Breastfeeding
In lactating rats, oseltamivir and the active metabolite are excreted in milk. Very limited information is available on children breast-fed by mothers taking oseltamivir and on excretion of oseltamivir in breast milk. Limited data demonstrated that oseltamivir and the active metabolite were detected in breast milk, however the levels were low, which would result in a subtherapeutic dose to the infant. Considering this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the breastfeeding woman, administration of oseltamivir may be considered, where there are clear potential benefits to breastfeeding mothers.

Fertility
Based on preclinical data, there is no evidence that Tamiflu has an effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Tamiflu has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The overall safety profile of Tamiflu is based on data from 6049 adult/adolescent and 1473 paediatric patients treated with Tamiflu or placebo for influenza, and on data from 3990 adult/adolescent and 253 paediatric patients receiving Tamiflu or placebo/no treatment for the prophylaxis of influenza in clinical trials. In addition, 245 immunocompromised patients (including 7 adolescents and 39 children) received Tamiflu for the treatment of influenza and 475 immunocompromised patients (including 18 children, of these 10 Tamiflu and 8 placebo) received Tamiflu or placebo for the prophylaxis of influenza.

In adults/adolescents, the most commonly reported adverse reactions (ARs) were nausea and vomiting in the treatment studies, and nausea in the prevention studies. The majority of these ARs were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2 days. In children, the most commonly reported adverse reaction was vomiting. In the majority of patients, these ARs did not lead to discontinuation of Tamiflu.

The following serious adverse reactions have been rarely reported since oseltamivir has been marketed: Anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice), angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding and neuropsychiatric disorders.
(Regarding neuropsychiatric disorders, see section 4.4.)

Tabulated list of adverse reactions
The ARs listed in the tables below fall into the following categories: 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*), and very rare (< *1/10,000*). ARs are added to the appropriate category in the tables according to the pooled analysis from clinical studies.

Treatment and prevention of influenza in adults and adolescents:
In adult/adolescent treatment and prevention studies, ARs that occurred the most frequently at the recommended dose (75 mg bid for 5 days for treatment and 75 mg od for up to 6 weeks for prophylaxis) are shown in Table 1.

The safety profile reported in subjects who received the recommended dose of Tamiflu for prophylaxis (75 mg once daily for up to 6 weeks) was qualitatively similar to that seen in the treatment studies, despite a longer duration of dosing in the prophylaxis studies.

Table 1 Adverse reactions in studies investigating Tamiflu for treatment and prevention of influenza in adults and adolescents or through post-marketing surveillance

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
Infections and infestations		Bronchitis, Herpes simplex, Nasopharyngitis, Upper respiratory tract infections, Sinusitis		
Blood and lymphatic system disorders				Thrombocytopenia
Immune system disorders			Hypersensitivity reaction	Anaphylactic reactions, Anaphylactoid reactions
Psychiatric disorders				Agitation, Abnormal behaviour, Anxiety, Confusion, Delusions, Delirium, Hallucination, Nightmares, Self-injury
Nervous system disorders	Headache	Insomnia	Altered level of consciousness, Convulsion	
Eye disorders				Visual disturbance
Cardiac disorders			Cardiac arrhythmia	
Respiratory, thoracic and mediastinal disorders		Cough, Sore throat, Rhinorrhea		
Gastrointestinal disorders	Nausea	Vomiting Abdominal pain (incl. upper abdominal pain), Dyspepsia		Gastrointestinal bleedings, Haemorrhagic colitis
Hepatobiliary disorders			Elevated liver enzymes	Fulminant hepatitis, Hepatic failure, Hepatitis
Skin and subcutaneous tissue disorders			Eczema, Dermatitis, Rash, Urticaria	Angioneurotic oedema, Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis
General disorders and administration site conditions		Pain Dizziness (incl. vertigo), Fatigue, Pyrexia,		

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
		Pain in limb		

Treatment and prevention of influenza in children:

A total of 1473 children (including otherwise healthy children aged 1-12 years old and asthmatic children aged 6-12 years old) participated in clinical studies of oseltamivir given for the treatment of influenza. Of those, 851 children received treatment with oseltamivir suspension. A total of 158 children received the recommended dose of Tamiflu once daily in a post-exposure prophylaxis study in households (n = 99), a 6-week paediatric seasonal prophylaxis study (n = 49) and a 12-week paediatric seasonal prophylaxis study in immunocompromised subjects (n = 10).

Table 2 shows the most frequently reported ARs from paediatric clinical trials.

Table 2 Adverse reactions in studies investigating Tamiflu for treatment and prevention of influenza in children (age/weight-based dosing [30 mg to 75 mg o.d.])

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
Infections and infestations		Otitis media,		
Nervous system disorders		Headache		
Eye disorders:		Conjunctivitis (including red eyes, eye discharge and eye pain)		
Ear and labyrinth disorders:		Earache	Tympanic membrane disorder	
Respiratory, thoracic and mediastinal disorders	Cough, Nasal congestion	Rhinorrhoea		
Gastrointestinal disorders	Vomiting	Abdominal pain (incl. upper abdominal pain), Dyspepsia, Nausea		
Skin and subcutaneous tissue disorders			Dermatitis (including allergic and atopic dermatitis)	

Description of selected adverse reactions

Psychiatric disorders and nervous system disorders
Influenza can be associated with a variety of neurologic and behavioural symptoms which can include events such as hallucinations, delirium, and abnormal behaviour, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.

In patients with influenza who were receiving Tamiflu, there have been postmarketing reports of convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares), in a very few cases resulting in self-injury or fatal outcomes. These events were reported primarily among paediatric and

adolescent patients and often had an abrupt onset and rapid resolution. The contribution of Tamiflu to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Tamiflu.

Hepato-biliary disorders
Hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness. These cases include fatal fulminant hepatitis/hepatic failure.

Other special populations

Paediatric population (infants less than one year of age)
In two studies to characterise the pharmacokinetics, pharmacodynamics and safety profile of oseltamivir therapy in 135 influenza infected children less than one year of age, the safety profile was similar among age cohorts with vomiting, diarrohea and diaper rash being the most frequently reported adverse events (see section 5.2). Insufficient data are available for infants who have a post-conceptual age of less than 36 weeks.

Safety information available on oseltamivir administered for treatment of influenza in infants less than one year of age from prospective and retrospective observational studies (comprising together more than 2,400 infants of that age class), epidemiological databases research and postmarketing reports suggest that the safety profile in infants less than one year of age is similar to the established safety profile of children aged one year and older.

Older people and patients with chronic cardiac and/or respiratory disease
The population included in the influenza treatment studies is comprised of otherwise healthy adults/adolescents and patients “at risk” (patients at higher risk of developing complications associated with influenza, e.g. older people and patients with chronic cardiac or respiratory disease). In general, the safety profile in the patients “at risk” was qualitatively similar to that in otherwise healthy adults/adolescents.

Immunocompromised patients

The treatment of influenza in immunocompromised patients were evaluated in two studies receiving standard dose or high dose regimens (double dose or triple dose) of Tamiflu (see section 5.1). The safety profile of Tamiflu observed in these studies was consistent with that observed in previous clinical trials where Tamiflu was administered for treatment of influenza in non-immunocompromised patients across all age groups (otherwise healthy patients or “at risk” patients [i.e., those with respiratory and/or cardiac co-morbidities]). The most frequent adverse reaction reported in immunocompromised children was vomiting (28%).

In a 12-week prophylaxis study in 475 immunocompromised patients, including 18 children 1 to 12 years of age and older, the safety profile in the 238 patients who received oseltamivir was consistent with that previously observed in Tamiflu prophylaxis clinical studies.

Children with pre-existing bronchial asthma
In general, the adverse reaction profile in children with pre-existing bronchial asthma was qualitatively similar to that of otherwise healthy children.

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

Reports of overdoses with Tamiflu have been received from clinical trials and during post-marketing experience. In the majority of cases reporting overdose, no adverse events were reported.

Adverse events reported following overdose were similar in nature and distribution to those observed with therapeutic doses of Tamiflu, described in section 4.8 Undesirable effects.

No specific antidote is known.

Paediatric population
Overdose has been reported more frequently for children than adults and adolescents. Caution should be exercised when preparing Tamiflu oral suspension and when administering Tamiflu products to children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors ATC code: J05AH02

Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity *in vivo* in animal models of influenza infection at antiviral exposures similar to that achieved in man with 75 mg twice daily.

Antiviral activity of oseltamivir was supported for influenza A and B by experimental challenge studies in healthy volunteers.

Neuraminidase enzyme IC50 values for oseltamivir for clinically isolated influenza A ranged from 0.1 nM to 1.3 nM, and for influenza B was 2.6 nM. Higher IC50 values for influenza B, up to a median of 8.5 nM, have been observed in published studies.

Clinical studies
Treatment of influenza infection
The indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A.Oseltamivir is effective only against illnesses caused by influenza virus. Statistical analyses are therefore presented only for influenza-infected subjects. In the pooled treatment study population, which included both influenza-positive and -negative subjects (ITT), primary efficacy was reduced proportionally to the number of influenza-negative individuals. In the overall treatment population, influenza infection was confirmed in 67 % (range 46 % to 74 %) of the recruited patients. Of the older subjects, 64 % were influenza-positive and of those with chronic cardiac and/or respiratory disease 62 % were influenza-positive. In all phase III treatment studies, patients were recruited only during the period in which influenza was circulating in the local community.

Adults and adolescents 13 years of age and older: Patients were eligible if they reported within 36 hours of onset of symptoms, had fever ≥ 37.8 °C, accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats,

malaise, fatigue or headache). In a pooled analysis of all influenza-positive adults and adolescents (N = 2,413) enrolled into treatment studies, oseltamivir 75 mg twice daily for 5 days reduced the median duration of influenza illness by approximately one day from 5.2 days (95 % CI 4.9 – 5.5 days) in the placebo group to 4.2 days (95 % CI 4.0 – 4.4 days; $p \leq 0.0001$).

The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7 % (135/1,063) in the placebo group to 8.6 % (116/1,350) in the oseltamivir treated population ($p = 0.0012$).

Treatment of influenza in high risk populations: The median duration of influenza illness in older subjects (≥ 65 years) and in subjects with chronic cardiac and/or respiratory disease receiving oseltamivir 75 mg twice daily for 5 days was not reduced significantly. The total duration of fever was reduced by one day in the groups treated with oseltamivir. In influenza-positive older people, oseltamivir significantly reduced the incidence of specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics from 19 % (52/268) in the placebo group to 12 % (29/250) in the oseltamivir treated population ($p = 0.0156$).

In influenza-positive patients with chronic cardiac and/or respiratory disease, the combined incidence of lower respiratory tract complications (mainly bronchitis) treated with antibiotics was 17 % (22/133) in the placebo group and 14 % (16/118) in the oseltamivir treated population ($p = 0.5976$).

Treatment of influenza in pregnant women: No controlled clinical studies have been conducted on the use of oseltamivir in pregnant women, however, there is evidence from post-marketing and retrospective observational studies showing benefit of the current dosing regimen in this patient population in terms of lower morbidity/mortality. Results from pharmacokinetic analyses indicate a lower exposure to the active metabolite, however dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza (see section 5.2, Pharmacokinetics, Special Population).

Treatment of influenza in children: In a study of otherwise healthy children (65 % influenza-positive) aged 1 to 12 years (mean age 5.3 years) who had fever (≥ 37.8 °C) plus either cough or coryza, 67 % of influenza-positive patients were infected with influenza A and 33 % with influenza B. Oseltamivir treatment, started within 48 hours of onset of symptoms, significantly reduced the time to freedom from illness (defined as the simultaneous return to normal health and activity and alleviation of fever, cough and coryza) by 1.5 days (95 % CI 0.6 – 2.2 days; $p < 0.0001$) compared to placebo. Oseltamivir reduced the incidence of acute otitis media from 26.5 % (53/200) in the placebo group to 16 % (29/183) in the oseltamivir treated children ($p = 0.013$).

A second study was completed in 334 asthmatic children aged 6 to 12 years old of which 53.6 % were influenza-positive. In the oseltamivir treated group, the median duration of illness was not reduced significantly. By day 6 (the last day of treatment) FEV_1 had increased by 10.8 % in the oseltamivir treated group compared to 4.7 % on placebo ($p = 0.0148$) in this population.

The European Medicines Agency has deferred the obligation to submit the results of studies with Tamiflu in one or more subsets of the paediatric population in influenza. See section 4.2 for information on paediatric use.
The indication in infants below the age of 1 is based upon extrapolation of efficacy data from older children and the recommended posology is based upon pharmacokinetic modelling data (see Section 5.2).

Treatment of influenza B infection: Overall, 15 % of the influenza-positive population were infected by influenza B, proportions ranging from 1 to 33 % in individual studies. The median duration of illness in influenza B infected subjects did not differ significantly between the treatment groups in individual studies. Data from 504 influenza B infected subjects were pooled across all studies for analysis. Oseltamivir reduced the time to alleviation of all symptoms by 0.7 days (95 % CI 0.1 – 1.6 days; $p = 0.022$) and the duration of fever (≥ 37.8 °C), cough and coryza by one day (95 % CI 0.4 – 1.7 days; $p < 0.001$) compared to placebo.

Treatment of influenza in immunocompromised patients: A randomized, double blind study, to evaluate safety and characterize the effects of oseltamivir on the development of resistant influenza virus (primary analysis) in influenza-infected immunocompromised patients, included 151 adult patients, 7 adolescents and 9 children evaluable for efficacy of oseltamivir (secondary analysis, not powered). The study included solid organ transplant [SOT] patients, haematopoietic stem cell transplant [HSCT] patients, HIV positive patients with a CD4+ cell count <500 cells/mm3, patients on systemic immunosuppressive therapy, and those with haematological malignancy. These patients were randomized to be treated, within 96 hours of symptoms onset for a duration of 10 days. The treatment regimens were: standard dose (75mg or weight-adjusted dose for children) twice daily (73 adult patients, 4 adolescent patients and 4 children) or double dose (150mg or weight-adjusted dose for children) twice daily (78 adult patients, 3 adolescent patients and 5 children) of oseltamivir.

The median time to resolution of symptoms (TTRS) for adults and adolescents was similar between the standard dose group (103.4 hours [95% CI 75.4-122.7]) and double dose group (107.2 hours [95% CI 63.9-140.0]). The TTRS for children was variable and the interpretation is limited by the small sample size.The proportion of adult patients with secondary infections in the standard dose group and double dose group was comparable (8.2% vs 5.1%). For adolescents and children, only one patient (an adolescent) in the standard dose group experienced a secondary infection (bacterial sinusitis).

A pharmacokinetics and pharmacodynamics study was conducted in severely immunocompromised children (≤12 years of age, n=30) receiving standard (75mg or weight adjusted twice daily) vs. triple dose (225mg or weight-adjusted dose twice daily) oseltamivir for an adaptive dosing period of 5 to 20 days dependent on duration of viral shedding (mean treatment duration: 9 days). No patients in the standard dose group and 2 patients in the triple dose group reported secondary bacterial infections (bronchitis and sinusitis).

Prevention of influenza
The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households and two seasonal prevention studies. The primary efficacy parameter for all of these studies was the incidence of laboratory-confirmed influenza. The virulence of influenza epidemics is not predictable and varies within a region and from season to season, therefore the number needed to treat (NNT) in order to prevent one case of influenza illness varies.

Post-exposure prevention: In a study in contacts (12.6 % vaccinated against influenza) of an index case of influenza, oseltamivir 75 mg once daily was started within 2 days of onset of symptoms in the index case and continued for seven days. Influenza was confirmed in 163 out of 377 index cases. Oseltamivir significantly reduced the incidence of clinical influenza illness occurring in the contacts of confirmed influenza cases from 24/200 (12 %) in the placebo group to 2/205 (1 %) in the oseltamivir group (92 % reduction [95 % CI 6 – 16; $p \leq 0.0001$]). The number needed to treat (NNT) in contacts of true influenza cases was 10 (95 % CI 9 – 12) and was 16 (95 % CI 15 – 19) in the whole population (ITT) regardless of infection status in the index case.

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, and children aged 1 to 12 years, both as index cases and as family contacts. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza in the households. Oseltamivir prophylaxis lasted for 10 days. In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20 % (27/136) in the group not receiving prevention to 7 % (10/135) in the group receiving prevention (62.7 % reduction [95 % CI 26.0 – 81.2; $p = 0.0042$]). In households of influenza-infected index cases, there was a reduction in the incidence of influenza from 26 % (23/89) in the group not receiving prevention to 11 % (9/84) in the group receiving prevention (58.5 % reduction [95 % CI 15.6 – 79.6; $p = 0.0114$]).
According to subgroup analysis in children at 1 to 12 years of age, the incidence of laboratory-confirmed clinical influenza among children was significantly reduced from 19 % (21/111) in the group not receiving prevention to 7 % (7/104) in the group receiving prevention (64.4 % reduction

[95 % CI 15.8 – 85.0; p = 0.0188]). Among children who were not already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was reduced from 21 % (15/70) in the group not receiving prevention to 4 % (2/47) in the group receiving prevention (80.1 % reduction [95 % CI 22.0 – 94.9; p = 0.0206]). The NNT for the total paediatric population was 9 (95 % CI 7 – 24) and 8 (95 % CI 6, upper limit not estimable) in the whole population (ITT) and in paediatric contacts of infected index cases (ITTII), respectively.

Post-exposure prevention of influenza in infants less than 1 year of age during a pandemic:
Prevention during an influenza pandemic has not been studied in controlled clinical studies in children 0-12 months of age. See Section 5.2 for exposure simulation details.

Prevention during an influenza epidemic in the community: In a pooled analysis of two other studies conducted in unvaccinated otherwise healthy adults, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 25/519 (4.8 %) in the placebo group to 6/520 (1.2 %) in the oseltamivir group (76 % reduction [95 % CI 1.6 – 5.7; p = 0.0006]) during a community outbreak of influenza. The NNT in this study was 28 (95 % CI 24 – 50).
A study in older people in nursing homes, where 80 % of participants received vaccine in the season of the study, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 12/272 (4.4 %) in the placebo group to 1/276 (0.4 %) in the oseltamivir group (92 % reduction [95 % CI 1.5 – 6.6; p = 0.0015]). The NNT in this study was 25 (95 % CI 23 – 62).

Prophylaxis of influenza in immunocompromised patients: A double-blind, placebo-controlled, randomised study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised patients (388 patients with solid organ transplantation [195 placebo; 193 oseltamivir], 87 patients with haemopoetic stem cell transplantation [43 placebo; 44 oseltamivir], no patient with other immunosuppressant conditions), including 18 children 1 to 12 years of age. The primary endpoint in this study was the incidence of laboratory-confirmed clinical influenza as determined by viral culture and/or a four-fold rise in HAI antibodies. The incidence of laboratory-confirmed clinical influenza was 2.9 % (7/238) in the placebo group and 2.1 % (5/237) in the oseltamivir group (95 % CI -2.3 % – 4.1 %; p = 0.772).

Specific studies have not been conducted to assess the reduction in the risk of complications.

Oseltamivir resistance
Clinical studies: The risk of emergence of influenza viruses with reduced susceptibility or frank resistance to oseltamivir has been examined during Roche-sponsored clinical studies. Developing oseltamivir-resistant virus during treatment was more frequent in children than adults, ranging from less than 1% in adults to 18% in infants aged below 1 year. Children who were found to carry oseltamivir-resistant virus in general shed the virus for a prolonged period compared with subjects with susceptible virus. However treatment-emergent resistance to oseltamivir did not affect treatment response and caused no prolongation of influenza symptoms.

An overall higher incidence of oseltamivir resistance was observed in adult and adolescent immunocompromised patients treated with standard dose or double dose of oseltamivir for a duration of 10 days [14.5% (10/69) in standard dose group and 2.7% (2/74) in double dose group], compared to data from studies with oseltamivir-treated otherwise healthy adult and adolescent patients. The majority of adult patients that developed resistance were transplant recipients (8/10 patients in the standard dose group and 2/2 patients in the double dose group). Most of the patients with oseltamivir-resistant virus were infected with influenza type A and had prolonged viral shedding.

The incidence of oseltamivir-resistance observed in immunocompromised children (≤12 years of age) treated with Tamiflu across the two studies and evaluated for resistance was 20.7% (6/29). Of the six immunocompromised children found with treatment-emergent resistance to oseltamivir, 3 patients received standard dose and 3 patients high dose (double or triple dose). The majority had acute lymphoid leukemia and were ≤ 5 years of age.

Incidence of Oseltamivir Resistance in Clinical Studies

Patient Population	Patients with Resistance Mutations (%)	
	Phenotyping*	**Geno- and Phenotyping***
Adults and adolescents	0.88% (21/2382)	1.13% (27/2396)
Children (1-12 years)	4.11% (71/1726)	4.52% (78/1727)
Infant (<1 year)	18.31% (13/71)	18.31 (13/71)

* Full genotyping was not performed in all studies.

Prophylaxis of Influenza
There has been no evidence for emergence of drug resistance associated with the use of Tamiflu in clinical studies conducted to date in post-exposure (7 days), post-exposure within household groups (10 days) and seasonal (42 days) prevention of influenza in immunocompetent patients. There was no resistance observed during a 12-week prophylaxis study in immunocompromised patients.

Clinical and surveillance data: Natural mutations associated with reduced susceptibility to oseltamivir *in vitro* have been detected in influenza A and B viruses isolated from patients without exposure to oseltamivir. Resistant strains selected during oseltamivir treatment have been isolated from both immunocompetent and immunocompromised patients. Immunocompromised patients and young children are at a higher risk of developing oseltamivir-resistant virus during treatment.

Oseltamivir-resistant viruses isolated from oseltamivir-treated patients and oseltamivir-resistant laboratory strains of influenza viruses have been found to contain mutations in N1 and N2 neuraminidases. Resistance mutations tend to be viral sub-type specific. Since 2007 naturally occurring resistance associated with the H275Y mutation in seasonal H1N1 strains has been sporadically detected. The susceptibility to oseltamivir and the prevalence of such viruses appear to vary seasonally and geographically. In 2008, H275Y was found in > 99 % of circulating H1N1 influenza isolates in Europe. The 2009 H1N1 influenza (“swine flu”) was almost uniformly susceptible to oseltamivir, with only sporadic reports of resistance in connection with both therapeutic and prophylactic regimens.

5.2 Pharmacokinetic properties

General Information

Absorption
Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic esterases to the active metabolite (oseltamivir carboxylate). At least 75 % of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5 % relative to the active metabolite. Plasma concentrations of both pro-drug and active metabolite are proportional to dose and are unaffected by co-administration with food.

Distribution
The mean volume of distribution at steady state of the oseltamivir carboxylate is approximately 23 litres in humans, a volume equivalent to extracellular body fluid. Since neuraminidase activity is extracellular, oseltamivir carboxylate distributes to all sites of influenza virus spread.

The binding of the oseltamivir carboxylate to human plasma protein is negligible (approximately 3 %).

Biotransformation
Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. *In vitro* studies demonstrated that neither oseltamivir nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. No phase 2 conjugates of either compound have been identified *in vivo*.

Elimination
Absorbed oseltamivir is primarily (> 90 %) eliminated by conversion to oseltamivir carboxylate. It is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18.8 l/h) exceeds glomerular filtration rate (7.5 l/h) indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20 % of an oral radiolabelled dose is eliminated in faeces.

Other special populations

Paediatric population
Infants less than 1 year of age: The pharmacokinetics, pharmacodynamics and safety of Tamiflu have been evaluated in two uncontrolled open-label studies including influenza infected children less than one year of age (n=135). The rate of clearance of the active metabolite, corrected for body-weight, decreases with ages below one year. Metabolite exposures are also more variable in the youngest infants. The available data indicates that the exposure following a 3 mg/kg dose in infants 0-12 months of age provides pro-drug and metabolite exposures anticipated to be efficacious with a safety profile comparable to that seen in older children and adults using the approved dose (see sections 4.1 and 4.2).The reported adverse events were consistent with the established safety profile in older children.

There are no data available for infants below 1 year of age for post exposure prevention of influenza. Prevention during an influenza epidemic in the community has not been studied in children below 12 years of age.

Post-exposure prevention of influenza in infants less than 1 year of age during a pandemic:
Simulation of once daily dosing of 3mg/kg in infants <1 year shows an exposure in the same range or higher than for once daily dosing of 75 mg in adults. Exposure does not exceed that for treatment of infants < 1 year (3 mg/kg twice daily) and is anticipated to result in a comparable safety profile (see Section 4.8). No clinical studies of prophylaxis in infants aged <1 have been performed.

Infants and children 1 year of age or older: The pharmacokinetics of oseltamivir have been evaluated in single-dose pharmacokinetic studies in infants, children and adolescents 1 to 16 years of age. Multiple-dose pharmacokinetics were studied in a small number of children enrolled in a clinical efficacy study. Younger children cleared both the pro-drug and its active metabolite faster than adults, resulting in a lower exposure for a given mg/kg dose. Doses of 2 mg/kg give oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children and adolescents 12 years of age or older are similar to those in adults.

Elderly
Exposure to the active metabolite at steady state was 25 to 35 % higher in older people (age 65 to 78 years) compared to adults less than 65 years of age given comparable doses of oseltamivir. Half-lives observed in older people were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for older people unless there is evidence of moderate or severe renal impairment (creatinine clearance below 60 ml /min) (see section 4.2).

Renal impairment
Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. For dosing, see section 4.2.

Hepatic impairment
In vitro studies have concluded that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment (see section 4.2).

Pregnant Women
A pooled population pharmacokinetic analysis indicates that the Tamiflu dosage regimen described in Section 4.2 Posology and method of administration results in lower exposure (30% on average across all trimesters) to the active metabolite in pregnant women compared to non-pregnant women. The lower predicted exposure however, remains above inhibitoy concentrations (IC95 values) and at a therapeutic level for a range of influenza virus strains. In addition, there is evidence from observational studies showing benefit of the current dosing regimen in this patient population. Therefore, dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza (see section 4.6 Fertility, pregnancy and lactation).

Immunocompromised Patients
Population pharmacokinetic analyses indicate that treatment of adult and paediatric (<18 years old) immunocompromised patients with oseltamivir (as described in Section 4.2. Posology and method of administration) results in an increased predicted exposure (from approximately 5% up to 50%) to the active metabolite when compared to non-immunocompromised patients with comparable creatinine clearance. Due to the wide safety margin of the active metabolite, no dose adjustments are required in patients due to their immunocompromised status. However, for immunocompromised patients with renal impairment, doses should be adjusted as outlined in section 4.2. Posology and method of administration.

Pharmacokinetics and pharmacodynamics analyses from two studies in immunocompromised patients indicated that there was no meaningful additional benefit in exposures higher than those achieved after the administration of the standard dose.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity. Results of the conventional rodent carcinogenicity studies showed a trend towards a dose-dependent increase in the incidence of some tumours that are typical for the rodent strains used. Considering the margins of exposure in relation to the expected exposure in the human use, these findings do not change the benefit-risk of Tamiflu in its adopted therapeutic indications.

Teratology studies have been conducted in rats and rabbits at doses of up to 1,500 mg/kg/day and 500 mg/kg/day, respectively. No effects on foetal development were observed. A rat fertility study up to a dose of 1,500 mg/kg/day demonstrated no adverse reactions on either sex. In pre- and post-natal rat studies, prolonged parturition was noted at 1,500 mg/kg/day: the safety margin between human exposure and the highest no-effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in the rats and rabbits was approximately 15 to 20 % of that of the mother.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. Limited data indicate that oseltamivir and the active metabolite are excreted in human milk. Extrapolation of the animal data provides estimates of 0.01 mg/day and 0.3 mg/day for the respective compounds.

A potential for skin sensitisation to oseltamivir was observed in a "maximisation" test in guinea pigs. Approximately 50 % of the animals treated with the unformulated active substance showed erythema after challenging the induced animals. Reversible irritancy of rabbits' eyes was detected.

Whereas very high oral single doses of oseltamivir phosphate salt, up to the highest dose tested (1,310 mg/kg), had no adverse reactions in adult rats, such doses resulted in toxicity in juvenile 7-day-old rat pups, including death. These reactions were seen at doses of 657 mg/kg and higher. At 500 mg/kg, no adverse reactions were seen, including upon chronic treatment (500 mg/kg/day administered from 7 to 21 days post partum).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420),
Sodium dihydrogen citrate (E331[a])
Xanthan gum (E415)
Sodium benzoate (E211)
Saccharin sodium (E954)
Titanium dioxide (E171)
Tutti frutti flavour (including maltodextrins [maize], propylene glycol, arabic gum E414 and natural identical flavouring substances [mainly consisting of banana, pineapple and peach flavour]).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

After reconstitution, store below 25 °C for 10 days.

6.4 Special precautions for storage

Do not store above 30°C.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

100 ml amber glass bottle (with child-resistant polypropylene screw cap, outer part: polyethylene; inner part: polypropylene; liner: polyethylene) with 13 g of powder for oral suspension, a plastic adapter (low density polyethylene) , plastic 3 ml oral dispenser (0.1 ml graduation) and 10 ml oral dispenser (0.5 ml graduation) (barrel and plunger: polypropylene, silicon based seal ring) and a plastic measuring cup (polypropylene).

Pack-size of one bottle.

6.6 Special precautions for disposal and other handling

It is recommended that Tamiflu oral suspension should be reconstituted by the pharmacist prior to being dispensed to the patient.

After reconstitution with 55 ml of water, the usable volume of oral suspension allows for the retrieval of a total of 10 doses of 30 mg oseltamivir.

<u>Preparation of oral suspension</u>
1. Tap the closed bottle gently several times to loosen the powder.
2. Measure 55 ml of water by filling the measuring cup to the indicated level (measuring cup included in the box).
3. Add all 55 ml of water into the bottle, recap the bottle and shake the closed bottle well for 15 seconds.
4. Remove the cap and push the bottle adapter into the neck of the bottle.
5. Close the bottle tightly with the cap (on the top of the bottle adapter). This will make sure that the bottle adapter fits in the bottle in the right position.

Tamiflu powder for suspension will appear as an opaque and white to light yellow suspension after reconstitution.

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/222/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 November 2011
Date of last renewal: 22 May 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu