Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Dexamethasone 20 mg Soluble Tablets

(dexamethasone sodium phosphate)

PL 35533/0169

Aspire Pharma Limited

LAY SUMMARY

Dexamethasone 20 mg Soluble Tablets (dexamethasone)

This is a summary of the Public Assessment Report (PAR) for Dexamethasone 20 mg Soluble Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this this product.

This product will be referred to as Dexamethasone Soluble Tablets in this lay summary for ease of reading.

For practical information about using Dexamethasone Soluble Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Dexamethasone Soluble Tablets and what are they used for?
This application is for a medicine that has a well-established use. This means that the use of the active substance in this medicine have been well-established in the United Kingdom (UK) for at least 10 years, with recognised efficacy and an acceptable level of safety.

This medicine is recommended for treating the following:
- rheumatic and autoimmune diseases (e.g. myositis)
- skin diseases (e.g. pemphigus vulgaris)
- blood disorders (e.g. idiopathic thrombocytopenic purpura in adults)
- treatment of symptomatic multiple myeloma, acute lymphoblastic leukaemia, Hodgkin's disease and non-Hodgkin's lymphoma in combination with other medicinal products
- metastatic spinal cord compression (pressure on the spinal cord nerves caused by a tumour)
- prophylaxis and treatment of nausea and vomiting caused by chemotherapy, within antiemetic treatment.

The patient may be using this medicine for a different reason. They should ask their doctor why this medicine has been prescribed for them.

How do Dexamethasone Soluble Tablets work?
Dexamethasone Soluble Tablets contain the active substance dexamethasone (as dexamethasone sodium phosphate), which belongs to a group of medicines called steroids ('corticosteroids'). Corticosteroids occur naturally in the body (produced by the cortex of the adrenal gland) and help to maintain health and well-being via anti-inflammatory, analgesic and anti-allergic effects which suppresses the immune system.

Boosting the body with extra corticosteroid (such as dexamethasone) is an effective way to treat various illnesses involving inflammation in the body.

Dexamethasone reduces this inflammation, which could otherwise go on making the patient's condition worse.

How are Dexamethasone Soluble Tablets used?
The pharmaceutical form of this medicine is soluble tablets and the route of administration is oral (taken by mouth).

The patient's doctor will prescribe the most appropriate dose to treat their patient's condition.

The tablets should be taken as a drink after dissolving them in a glass of water. The patient should take their tablets as a **single dose each morning**, unless their doctor has told them otherwise.

Dexamethasone Soluble Tablets should be taken with or after food to minimise irritation to the gastrointestinal tract. Drinks containing alcohol or caffeine should be avoided.

The patient should be aware that this is a high dosage medical product.

Dexamethasone Soluble Tablets are recommended to be used at the lowest effective dose, recommended by your doctor.

Adults:
The usual dose of dexamethasone is 0.5 mg to 10 mg daily, depending on the disease being treated. In more severe disease conditions, doses above 10 mg per day may be required. The dose should be titrated to the individual patient response and disease severity. In order to minimise side effects, the lowest effective possible dose should be used. The patient's doctor will decide their exact dose based on how serious the patient's illness is.

Unless otherwise prescribed, the following dosage recommendations apply:
The below mentioned dosing recommendations are given for guidance only. The initial and daily doses should always be determined based on individual patient response and disease severity.

- **Pemphigus:** initial dose of 300 mg for three days followed by down titration according to clinical need..
- **Myositis:** 40 mg for 4 days in cycles..
- **Idiopathic thrombocytopenic purpura:** 40 mg for 4 days in cycles.
- **Metastatic spinal cord compression:** initial dose and duration of treatment depending on the cause and severity. Very high doses up to 96 mg may be used for palliative treatment. For optimal dosing and reduction of the number of tablets the combination of lower dose strengths (4 mg and 8 mg) and higher dose strengths (20 mg or 40 mg) can be used.
- **Prophylaxis and treatment of emesis induced by cytostatic, emetogenic chemotherapy within antiemetic treatment:** 8 mg -20 mg (one 20mg tablet or one half of 40mg tablet) prior to chemotherapy treatment, then 4 mg -16mg/day on day 2 and 3.
- **Treatment of symptomatic multiple myeloma, acute lymphocytic leukaemia, acute lymphoblastic leukaemia, Hodgkin's disease and non-Hodgkin's lymphoma in combination with other medicinal products:** the usual posology is 40 mg or 20 mg once per day.

The dose and administration frequency vary with the therapeutic protocol and the associated treatment(s). Dexamethasone administration should follow instructions for dexamethasone administration when described in the SmPC of the associated treatment(s). If this is not the case, local or international treatment protocols and guidelines should be followed.
Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

Long-term treatment
For the long-term treatment of several conditions, after initial therapy, glucocorticoid treatment should be switched from dexamethasone to prednisone/prednisolone to reduce suppression on the function of the adrenal cortex.

Use in children: a single dose on alternate days**.**

Important: if a child is taking this medicine, it is important that the doctor monitors their growth and development at frequent intervals.

The patient should not exceed or take less than the stated dose.

The patient should not take it more or less often than prescribed.

For further information on how Dexamethasone Soluble Tablets are used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them.

The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Dexamethasone Soluble Tablets have been shown in studies?
As the active substance, dexamethasone (as dexamethasone sodium phosphate), has been in clinical use for over 10 years, data were provided in the form of literature references and the results of a bridging pharmacokinetic study to show that Dexamethasone Soluble Tablets are a safe and efficacious treatment for the proposed indications.

What are the possible side effects of Dexamethasone Soluble Tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for ‘MHRA Yellow Card’ online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why were Dexamethasone Soluble Tablets approved?
It was concluded that the data provided from literature references and the pharmacokinetic bridging study have shown that Dexamethasone Soluble Tablets are effective in the treatment of the proposed indications. Furthermore, the well-established use of the active substance dexamethasone has shown that it has recognised efficacy and an acceptable level of safety.

Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Dexamethasone Soluble Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Dexamethasone Soluble Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Dexamethasone Soluble Tablets
A Marketing Authorisation for Dexamethasone Soluble Tablets was granted in the UK on 20 October 2021.

The full PAR for Dexamethasone Soluble Tablets follows this summary.

This summary was last updated in December 2021.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Dexamethasone 20 mg Soluble Tablets (PL 35533/0169) could be approved.

The product is approved for the following indications:

Dermatology
Pemphigus vulgaris

Autoimmune disorders/rheumatology
Myositis

Haematological disorder
Idiopathic thrombocytopenic purpura in adults.

Oncology
Metastatic spinal cord compression.

Prophylaxis and treatment of emesis induced by cytostatics, emetogenic chemotherapy within antiemetic treatment.

Treatment of symptomatic multiple myeloma, acute lymphocytic leukemia, acute lymphoblastic leukemia, Hodgkin's disease and non-Hodgkin's lymphoma in combination with other medicinal products.

The active substance, dexamethasone, is a highly potent and long-acting glucocorticoid with negligible sodium retaining properties and is therefore, particularly suitable for the use in patients with cardiac failure and hypertension.

Its anti-inflammatory potency is seven times greater than prednisolone and, like other glucocorticoids, dexamethasone also has anti-allergic, antipyretic and immunosuppressive properties.

This application was approved under Regulation 54 of The Human Medicines Regulation 2012, as amended (previously Article 10a of Directive 2001/83/EC, as amended), as a well-established use application. A number of oral (including the proposed dosage form of soluble tablets) and parenteral formulations of dexamethasone are approved in the UK for the treatment of a wide range of clinical conditions.

No new non-clinical studies were submitted, as the data submitted for this application are in the form of literature references and the results from a new comparative bioavailability study, which bridge the product with the literature data.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A national Marketing Authorisation was granted in the United Kingdom (UK) on 20 October 2021.

II QUALITY ASPECTS

II.1 Introduction

This product contains 20 mg of dexamethasone (as dexamethasone sodium phosphate) in each soluble tablet.

In addition to dexamethasone, this product also contain the excipients sodium hydrogen carbonate, disodium hydrogen citrate, erythrosine (E127), povidone (K30), sodium saccharin and sodium benzoate (E211).

The finished product is packaged in polyamide/aluminium/polyvinylchloride/aluminium (PA/Al/PVC/aluminium) blisters, in pack sizes 10, 28, 30, 50, 56, 60 and 100 tablets.

Not all pack sizes may be marketed.

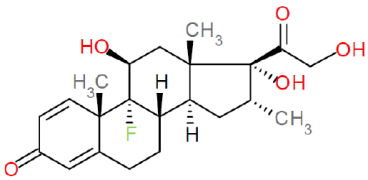
II.2 ACTIVE SUBSTANCE

rINN: Dexamethasone sodium phosphate

Chemical Name: Disodium 9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl phosphate

Molecular Formula: $C_{22}H_{29}FO_5$

Chemical Structure:



Molecular Weight: 516.4 g/mol

Appearance: White or almost white, very hygroscopic powder

Solubility: Practically insoluble in water, sparingly in anhydrous ethanol and freely soluble in dimethylformamide

Dexamethasone sodium phosphate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months, with the storage conditions 'Do not store above 25°C Store in the original blister to protect from moisture.', is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
This application was submitted under Regulation 54 of The Human Medicines Regulations 2012, as amended, as a well-established use application. No new non-clinical studies were submitted, as the data submitted for this application is in the form of literature references and the results of a clinical bioavailability bridging study. The literature review provided is satisfactory.

III.2 Pharmacology
No new pharmacology data were submitted, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were submitted, and none were required for this application.

III.4 Toxicology
No new toxicology data were submitted, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a product containing an active substance of well-established use that will be used in place of existing product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of dexamethasone are well known.

With the exception of the data from the pharmacokinetic bridging study, no new clinical studies were submitted, as the data submitted for this application is mainly in the form of literature references. The literature review provided is satisfactory.

The study was conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

The pharmacokinetics of dexamethasone are well-known. The Applicant has provided an adequate summary to support the respective sections of the proposed SmPC. A summary of the data provided in the clinical overview is present below.

Absorption

- **Bioavailability**

Dexamethasone is readily absorbed from the gastrointestinal tract. The high permeability of dexamethasone is characteristic of its pharmacological class (corticosteroids), which are generally accepted to be readily absorbed from the gastrointestinal tract. The bioavailability of dexamethasone is about 76 % (61 % - 86 %). However these values are in contrast with the reported fraction of dose absorbed, which lies in the range of 95 % - 100 %.

The permeability of dexamethasone has been calculated at about 95 % in Caco-2 cells.

Distribution

Animal studies indicate that most glucocorticoids are rapidly removed from the blood and distributed to muscles, liver, skin, intestines, and kidneys. Glucocorticoids vary in the extent to which they are bound to plasma proteins. Dexamethasone is bound (up to 77 %) to plasma proteins, mainly albumin. Percentage protein binding of dexamethasone, unlike that of cortisol, remains practically unchanged with increasing steroid concentrations.

Elimination

Dexamethasone is primarily metabolised in the liver. The inactive metabolites are excreted in the urine, mainly as glucuronides and sulphates, but also as unconjugated metabolites. Small amounts of unchanged drug are also excreted in the urine. Up to 65 % of a dose of dexamethasone is excreted in the urine within 24 hours. The elimination half-life of dexamethasone is 4.6 hrs, leading to no accumulation in the blood.

Pharmacokinetics in target population

None.

Special populations

- **Pregnancy and lactation**

In one study, the results obtained in pregnant women are similar to those reported by other workers in studies of healthy volunteers and non-pregnant patients, suggesting that the maternal pharmacokinetics of dexamethasone are unaltered in pregnancy with relative bioavailability of oral dexamethasone as 70 % of that achieved with intramuscular administration. The drug does, however, cross the placenta yielding pharmacologically significant plasma levels in the foetus, with consequent implications for both therapeutic and unwanted effects.

Interactions
The Applicant has provided a summary of the potential drug-drug interactions (pharmacokinetic and pharmacodynamic) for dexamethasone.

To further support of the application, the applicant submitted the following bridging pharmacokinetic study.

Bioequivalence study (single-dose, fasting conditions)
This study was an open-label, randomised, single dose, two-treatment, two-period, crossover, oral bioequivalence study comparing the Test product Dexamethasone 20 mg Soluble Tablets with the Reference product Dexamethasone Tablets BP 2 mg (2 mg x 10 tablets) in normal healthy, adult human subjects under fasting conditions.

Subjects were administered a single dose (20 mg) of the test product (20 mg x 1 tablet) or reference product (2 mg x 10 tablets), following an overnight fast of at least 10 hours. The test product was administered orally by dissolving the 20 mg tablet in 120 mL of water, followed by rinsing the glass with another 120 mL of water which was ingested after rinsing the mouth. The reference product was administered orally as 20 tablets (total dose = 20 mg) with 240 mL water (+160 mL). Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 14 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1: Geometric means, ratios and 90% Confidence Intervals (CIs) for pharmacokinetic parameters

Parameters (Units)	Geometric Least Squares Means and ratio (N = 32)			Intra subject %CV	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R)%			
AUC_{0-t} (hr*ng/mL)	1512.541	1540.116	98.21	6.96	95.35% - 101.15%	100.00
C_{max} (ng/mL)	308.301	254.192	121.29	13.22	114.70% - 128.25%	100.00

C_{max} Maximum drug concentration during the selected dosing interval
AUC_{0-t} Area under the plasma concentration versus time curve from time 0 to t

The pharmacokinetic study demonstrated that the 90% confidence intervals for the AUC_{0-t} ratio were within the bioequivalence acceptability limits and AUC_{0-t} was comparable between the Test and Reference products, however for C_{max} the upper bound of the 90% confidence intervals for the Test/Reference ratio was greater than the 125.00% limit. This is not completely unexpected as the Test product is administered as oral solution compared to the tablet form for the Reference product. A quicker T_{max} was also observed for the Test product compared to the Reference product.

The Applicant's argument is acceptable, in principle, that the observed difference in the peak exposure between the test and reference products is of unlikely relevance, especially in terms of the impact on the safety profile, and in the context of the chosen legal basis for this application, where demonstration of bioequivalence is not a strict regulatory requirement/ Therefore is accepted that the pharmacokinetic results showed that the test product (20 mg x 1 tablet) can be considered similar to the reference product (2 mg x 10 tablets).

In addition, the Applicant has provided an adequate discussion on the available bibliographic evidence to support the claim that the active substance (dexamethasone sodium phosphate) exhibits linear pharmacokinetics over the proposed dose range.

It is, therefore, concluded that the pharmacokinetic evidence provided by the Applicant is adequate to establish a bridge to the bibliographic evidence.

IV.3 Pharmacodynamics

The clinical pharmacodynamics of dexamethasone is well-characterised in the published literature. The Applicant has provided an adequate summary of bibliographic data available on the clinical pharmacodynamics of dexamethasone in the proposed indications.

Glucocorticoids, including dexamethasone, exert their actions principally via intracellular receptors, which belong to the nuclear receptor superfamily and regulate the transcription of target genes. The biological actions of the steroids are, thus, generally slow in onset and persist for some time after the steroid has been cleared from the circulation. Glucocorticoids produce their effects through their actions on the intracellular glucocorticoid receptors, which exists in virtually all cells to directly, or indirectly, regulate the transcription of certain target genes. The target gene can be transactivated or transrepressed. The number of genes per cell directly regulated by glucocorticoids is estimated between 10 and 100 and some others are indirectly regulated.

IV.4 Clinical efficacy

The clinical efficacy of dexamethasone is well-characterised in the published literature.

The Applicant has described, in the clinical overview, evidence from published literature in to support the clinical efficacy of the active substance in the proposed indications.

IV.5 Clinical safety

The safety of dexamethasone is well-characterised in the published literature.

The Applicant has provided an adequate summary of bibliographic data available on the clinical safety of dexamethasone in the proposed indications.

No new or unexpected safety concerns were raised from the safety data submitted with the clinical study.

IV.6 Risk Management Plan (RMP)

The Applicant has submitted a RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulations 2012, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The evidence provided from the comparative bioavailability study is deemed adequate to allow bridging to the bibliographic evidence. Refer to the pharmacokinetic study conclusions in section IV. 2, Pharmacokinetics.

The grant of a Marketing Authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified from the literature. Extensive clinical experience with dexamethasone is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

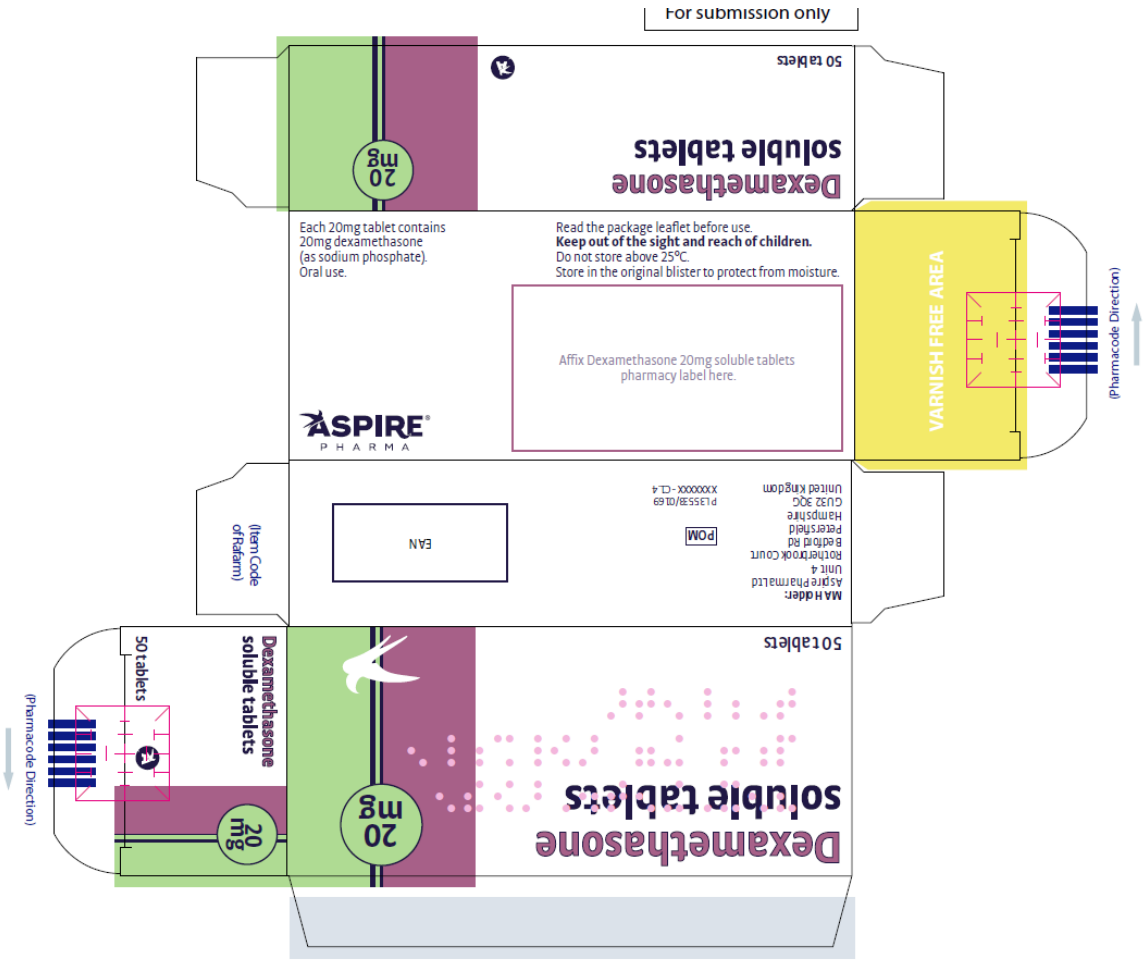
The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product is available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.

Dexamethasone 20 mg Soluble Tablets




For submission only
50 tablets
Dexamethasone
soluble tablets
20 mg
Each 20mg tablet contains
20mg dexamethasone
(as sodium phosphate).
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25°C.
Store in the original blister to protect from moisture.
Affix Dexamethasone 20mg soluble tablets pharmacy label here.
ASPIRE PHARMA
VARNISH FREE AREA
(Pharmacode Direction)
EAN
POM
(Item Code of Pafarm)
MA Holder:
Aspire Pharma Ltd
Unit 4
Rotherbrook Court
Bedford Rd
Petersfield
Hampshire
GU32 3QG
United Kingdom
Dexamethasone soluble tablets
50 tablets
20 mg
(Pharmacode Direction)

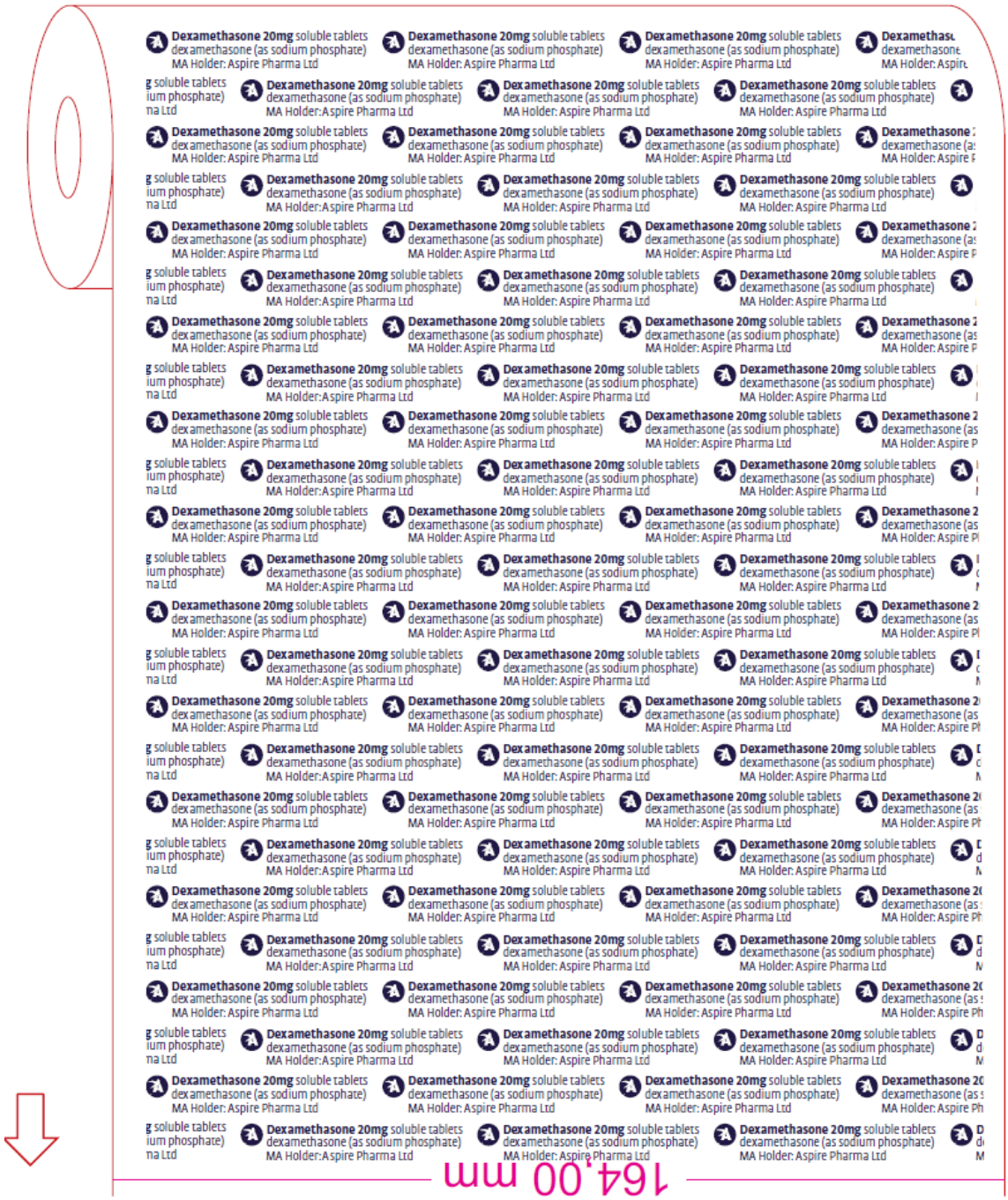

Dexamethasone 20mg soluble tablets
dexamethasone (as sodium phosphate)
MA Holder: Aspire Pharma Ltd
164.00 mm

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the Marketing Authorisations are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**