Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Desmopressin 60 mcg sublingual tablets
PL 44710/0035

Desmopressin 120 mcg sublingual tablets
PL 44710/0036

Desmopressin 240mcg sublingual tablets
PL 44710/0037

UKPAR

KINEDEXE UK LIMITED

Medicines and Healthcare Products Regulatory Agency

Desmopressin 60 mcg sublingual tablets PL 44710/0035

Desmopressin 120 mcg sublingual tablets PL 44710/0036

Desmopressin 240mcg sublingual tablets PL 44710/0037

LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Desmopressin 60, 120 & 240 micrograms sublingual tablets (PL 44710/0035-0037). It explains how Desmopressin 60, 120 & 240 micrograms sublingual tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Desmopressin 60, 120 & 240 micrograms sublingual tablets, patients should read the Patient Information Leaflet (PIL) available on the MHRA website or contact their doctor or pharmacist. For ease of reading, these products will be referred to as Desmopressin sublingual tablets throughout the rest of this lay summary.

What are Desmopressin sublingual tablets and what are they used for?
Desmopressin sublingual tablets contain 60, 120 or 240 micrograms of desmopressin (as acetate).

These medicines are used to treat:

- diabetes insipidus (extreme thirst and the continuous production of large volumes of dilute urine). IMPORTANT: This should not be confused with diabetes mellitus (sugar diabetes)
- post-hypophysectomy polyuria/polydipsia (extreme thirst and the continuous production of large volumes of dilute urine following surgical removal of the pituitary gland)

The 120 and 240 microgram tablets are also used to treat:

- Primary nocturnal enuresis (bedwetting) in children (from 5 years of age) and adults (up to 65 years of age).

How do Desmopressin sublingual tablets work?
These medicines belong to a group of medicines called vasopressin and analogues, it is an antidiuretic i.e. it reduces urine production.

How are Desmopressin sublingual tablets used?
Desmopressin sublingual tablets are intended for sublingual use (under the tongue). The tablet should be placed under the tongue and allowed to dissolve. Do not swallow or chew or take with water.

Always take Desmopressin sublingual tablets exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

For further information on how Desmopressin sublingual tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPC(s)) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take these medicines exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

How have Desmopressin sublingual tablets been studied?
Because Desmopressin sublingual tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Desmopressin sublingual tablets?
For the full list of all side effects reported with these medicines, 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.

Because Desmopressin sublingual tablets are generic medicines and are bioequivalent to the reference medicines, its benefits and possible side effects are considered to be the same as the reference medicines.

Why are Desmopressin sublingual tablets approved?
It was concluded that, Desmopressin sublingual tablets have been shown to be comparable to and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicines, 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 Desmopressin sublingual tablets?
A Risk Management Plan (RMP) has been developed to ensure that Desmopressin sublingual tablets is 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 Desmopressin sublingual tablets
Marketing Authorisations for Desmopressin sublingual tablets were granted in the United Kingdom (UK) on 24 March 2021.

The full PAR for Desmopressin sublingual tablets follows this summary.

This summary was last updated in May 2021.

Desmopressin 60 mcg sublingual tablets
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PL 44710/0037

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA considered that the applications for Desmopressin 60, 120 & 240 micrograms sublingual tablets (PL 44710/0035-0037) could be approved.

These products are prescription-only medicines (legal status "POM") intended for the treatment of vasopressin-sensitive cranial diabetes insipidus or in the treatment of post-hypophysectomy polyuria/polydipsia.

Desmopressin 120 & 240 micrograms sublingual tablets are also indicated for the treatment of primary nocturnal enuresis.

These products contain desmopressin acetate, a synthetic version of vasopressin.

These applications were submitted under Regulation 51 of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, DDAVP Melt 60, 120 & 240mcg Oral Lyophilisate (PL 03194/0091-93), that have been licensed within the UK for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application(s) is/are for a generic medicinal product(s) of a suitable reference product(s).

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. The bioequivalence studies were conducted in-line with current Good Clinical Practice (GCP).

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

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

National marketing authorisations were granted in the UK on 24 March 2021.

II QUALITY ASPECTS

II.1 Introduction

These products consist of 60, 120 & 240 micrograms of desmopressin (as an acetate).

In addition to desmopressin acetate, these products also contain the excipients citric acid monohydrate, mannitol, crospovidone, aspartame (E951), talc and sodium stearyl fumarate.

The finished products are packaged in high-density polyethylene bottles with child-resistant in pack sizes of 30, 40 and 100 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

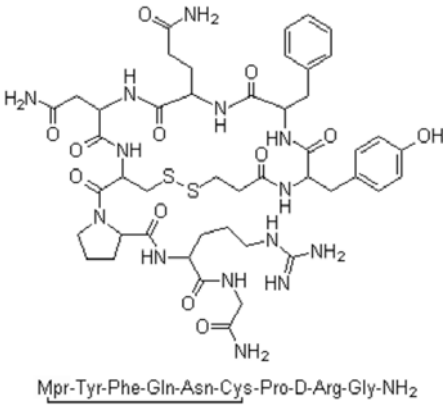
II.2 ACTIVE SUBSTANCE

rINN: Desmopressin

Chemical Name: *1-(3-Mercaptopropionic acid)-8-D-arginine-vasopressin; [1-Deamino,8-Darginine]vasopressin*

Molecular Formula: $C_{46}H_{64}N_{14}O_{12}S_2$

Chemical Structure:



Molecular Weight: 1069.22g/mol

Appearance: White or almost white, fluffy powder

Solubility: Soluble in water, in ethanol (96%) and in glacial acetic acid

Either

Desmopressin 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(S)

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

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 final products.

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

Manufacture of the product(s)
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, 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 12 months (reducing to 1 month once opened, with the storage conditions “protect from light”, “store in the original package”, “do not store above 25 degrees” and “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 marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of desmopressin are well-known, no new non-clinical studies were required and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of desmopressin is well-known. With the exception of data from the two bioequivalence studies undertaken, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of these studies is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following:

Pilot Bioequivalence Study
The results of a pilot bioequivalence study were submitted that failed to show bioequivalence against the innovator since AUC_{0-t} fell outside the standard 80-125% confidence interval (CI) bounds (though C_{max} was within the widened CI parameters permitted for a percentage cumulative variance (CV%) of 43.33%). On the basis of this pilot study, although bioequivalence was not seen (for AUC_{0-t}), the Applicant decided that progression to the definitive study could take place with the same formulation.

A summary of the pharmacokinetic results is presented below:

Parameters	Cmax (pg/ml)	AUC_{0-t} (hr*pg/ml)	$AUC_{0-\infty}$ (hr*pg/ml)	Power
T1/R Ratio	99.05	93.85	94.15	85.63
90% CI lower	79.55	77.34	78.10	60.20
90% CI Upper	123.34	113.88	113.50	62.83

Parameters	Cmax (pg/ml)	AUC 0-t (hr*pg/ml)	AUC 0-∞ (hr*pg/ml)
% ISCV of Reference	43.33	36.63	35.38
Widened CI for Cmax	72.96 to 137.06		

On the basis of this pilot study, although bioequivalence was not seen (for AUC_{0-t}), a further bioequivalence study was undertaken.

Pivotal Bioequivalence Study
This study was an open-label, balanced, randomized, single-dose, two-treatment, three-sequence, three-period, crossover bioequivalence study comparing the test product Desmopressin 240 microgram sublingual tablets (Kinedexe UK Limited) versus the reference product DDAVP Melt (desmopressin acetate) 240 microgram oral lyophilisate (Ferring Pharmaceuticals Limited) in subjects under fasted conditions.

Subjects were administered 480 micrograms (i.e. two sublingual 240 microgram tablets) of either the test or reference product after a 10-hour overnight fast. Blood samples were taken pre-dose and up to 16 hours post dose, with a washout period of 5 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Parameters (units)	Geometric Least Square Means		Ratio (%) (T Vs R)	90% Confidence Intervals (%)	Intra Subject CV of Reference formulation (%)	Power (T Vs R) (%)
	T (N=41)	R (N=81)				
Ln (C_{max}) (pg/ml)	74.051	76.398	96.93	88.82% - 105.77%	26.59	99.43
Ln (AUC_{0-t}) (hr *pg/ml)	297.967	316.552	94.13	87.06% - 101.78%	23.44	99.86

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the 60 microgram and 120 microgram strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the product strength can be extrapolated to the other strengths.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence studies, no new safety data were submitted with these applications.

The safety data from the bioequivalence studies showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 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 grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with the requirements of Regulation 267 of The Human Medicines Regulations 2012, as amended (previously article 61(1) of Council Directive 2001/83/EC).

The PIL has been evaluated via a user consultation study, in accordance with the requirements of Regulation 260(3) of The Human Medicines Regulation 2012, as amended (previously Article 59(3) of Council Directive 2001/83/EC). 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.

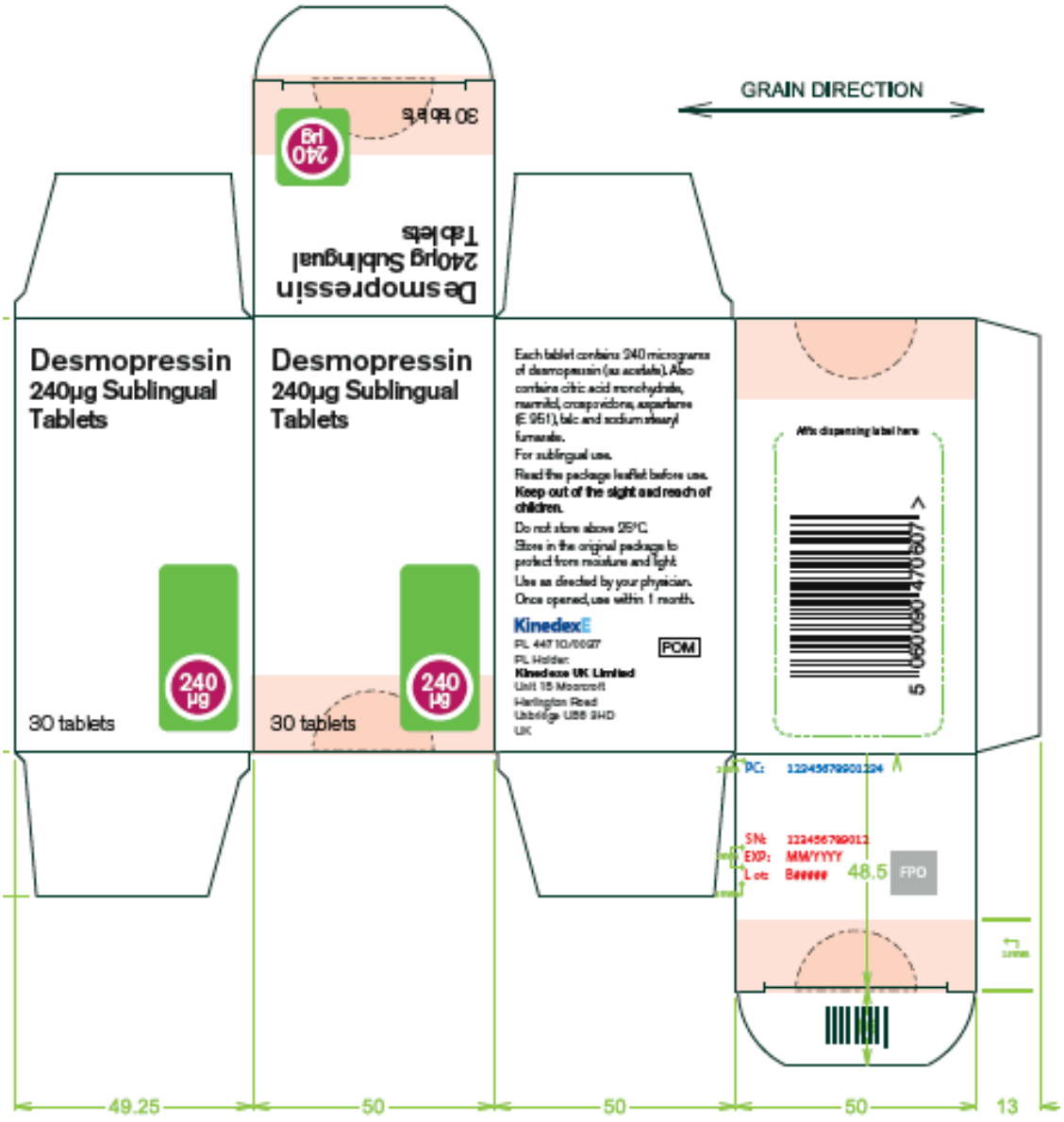
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with desmopressin 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, in line with current guidelines and consistent with the reference products.

In accordance with Regulation 203(2) of The Human Medicines Regulation 2012, as amended, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

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


GRAIN DIRECTION
Desmopressin
240µg Sublingual
Tablets
30 tablets
240 µg
Each tablet contains 240 micrograms of desmopressin (as acetate). Also contains citric acid monohydrate, mannitol, crospovidone, aspartame (E 951), talc and sodium stearyl fumarate.
For sublingual 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 package to protect from moisture and light.
Use as directed by your physician.
Once opened, use within 1 month.
KinedexE
PL 44710/0037
PL Holder:
Kinedexe UK Limited
Unit 15 Moorcroft
Harlington Road
Uxbridge UB8 3HD
UK
POM
Affix dispensing label here
(01)
PC:
SN:
EXP:
Lot:
48.5
FPO
49.25
50
50
50
13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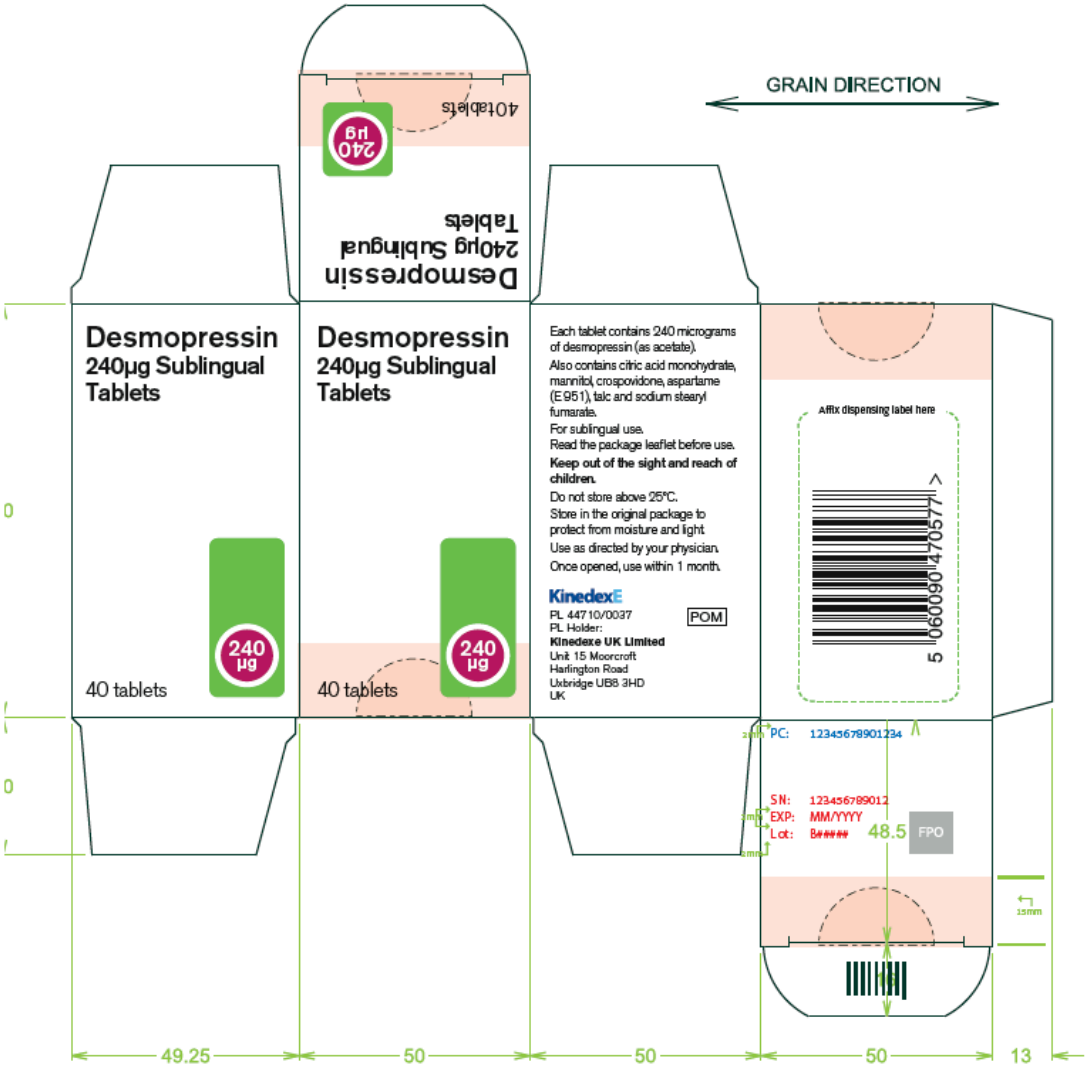
KinedexE
PL 44710/0037
PL Holder: Kinedexe UK Limited
Unit 15 Moorcroft, Harlington Road
Uxbridge UB8 3HD, UK
40 mm
110 mm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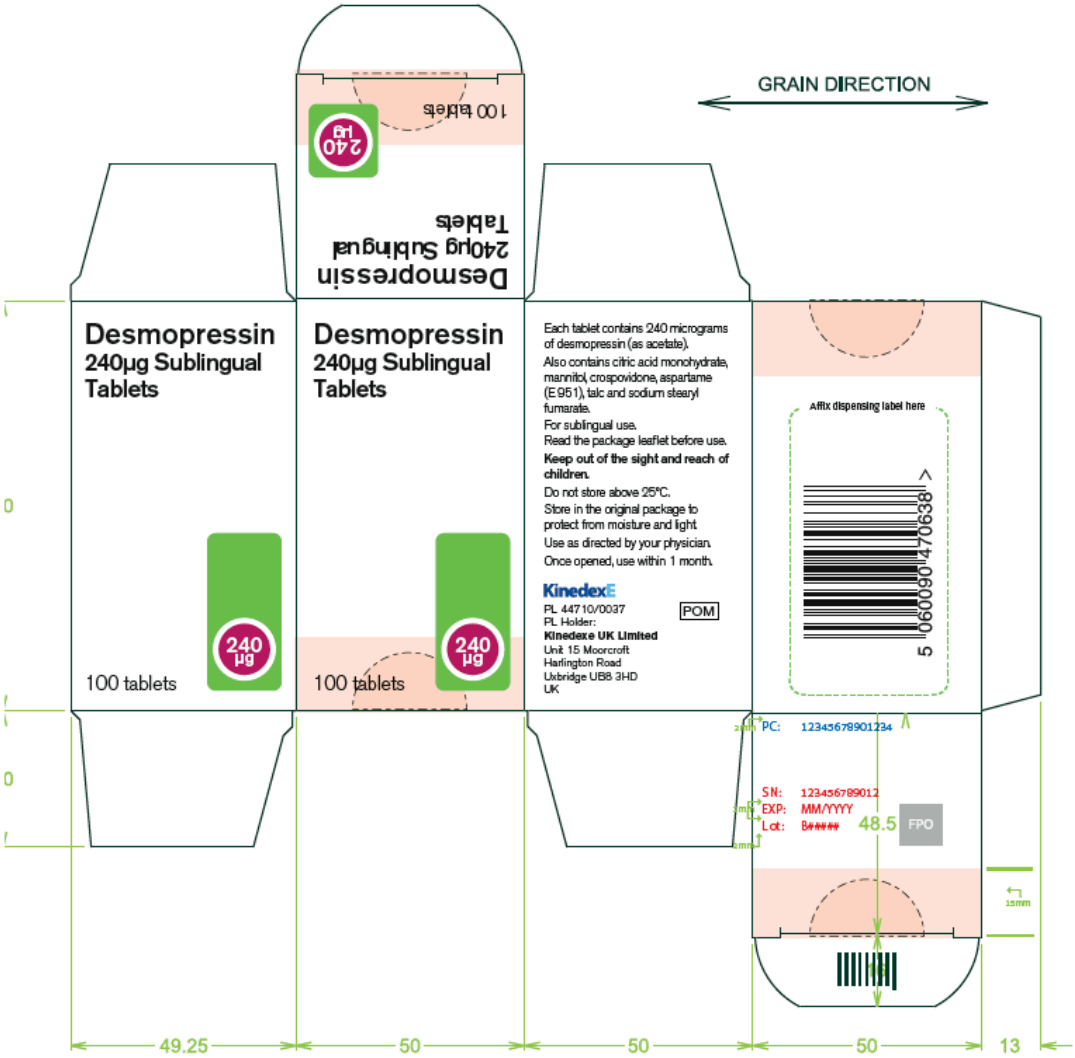
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SN: 123456789012
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TABLE OF CONTENT OF THE PAR UPDATE

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 authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

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