Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Budesonide 3 mg prolonged-release capsules (budesonide)

PL 47026/0006

Medical Valley Invest AB

LAY SUMMARY

Budesonide 3 mg prolonged-release capsules (budesonide)

This is a summary of the Public Assessment Report (PAR) for Budesonide 3 mg prolonged-release capsules. 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 product.

This product will be referred to as Budesonide prolonged-release capsules in this lay summary for ease of reading.

For practical information about using Budesonide prolonged-release capsules, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Budesonide prolonged-release capsules and what are they used for?
This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the United Kingdom (UK) called Entocort CR 3 mg Capsules.

Budesonide prolonged-release capsules are used in the treatment of:
- Crohn's disease: Budesonide prolonged-release capsules are used to treat an inflammation of the small bowel and the first part of the large bowel.
- Microscopic colitis: Budesonide prolonged-release capsules are used to treat microscopic colitis (a disease with chronic inflammation of the large bowel which is typically with chronic watery diarrhoea).

How do Budesonide prolonged-release capsules work?
This medicine contains the active substance budesonide. This belongs to a group of medicines called 'corticosteroids'. These are used to reduce inflammation.

How are Budesonide prolonged-release capsules used?
The pharmaceutical form of this medicine is prolonged-release capsules and the route of administration is oral (taken by mouth).

Crohn's disease
The recommended dose for an attack of Crohn's disease is 3 capsules in the morning before breakfast. Normally, the patient will take this number of capsules for up to 8 weeks. The patient's doctor will then gradually reduce the dose. The medicine will usually have its full effect within 2 to 4 weeks. The patient should continue to take Budesonide as their doctor has told them, even if they start feeling better.

Microscopic colitis:
For treatment of active disease: Take 3 capsules once daily in the morning. When treatment is to be discontinued, the dose should normally be reduced for the last 2 to 4 weeks of therapy.

For the maintenance of remission: Take 2 capsules once daily in the morning (or the lowest effective dose).

Use in children
Budesonide prolonged-release capsules are not recommended for children.

Additional information about taking Budesonide prolonged-release capsules

- If the patient is about to have an operation or during times of stress, they should tell the doctor that they are taking Budesonide prolonged-release capsules.
  The doctor may ask the patient to take steroid tablets as well, particularly if the patient has been taking a high dose of Budesonide prolonged-release capsules, or a similar medicine, for a long time.

- The patient should try to avoid people who have chicken pox or measles while they are taking Budesonide prolonged-release capsules. The patient should talk to their doctor if they think that they may have caught chicken pox or measles while taking this medicine.

For further information on how Budesonide prolonged-release capsules 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 this 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 Budesonide prolonged-release capsules have been shown in studies?
As Budesonide prolonged-release capsules are a hybrid medicine, studies in healthy volunteers consist of tests to determine that they are therapeutically equivalent to the reference medicine.

What are the possible side effects of Budesonide prolonged-release capsules?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC 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.

As Budesonide prolonged-release capsules are a hybrid medicine and is therapeutically equivalent to the reference medicine, possible side effects are taken as being the same as the reference medicine.

Why was Budesonide prolonged-release capsules approved?
It was concluded that Budesonide prolonged-release capsules have been shown to be therapeutically equivalent to the reference medicine. Therefore, the have MHRA decided that, as for the reference medicine, 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 Budesonide prolonged-release capsules?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Budesonide prolonged-release capsules The RMP details the important risks of Budesonide prolonged-release capsules, how these risks can be minimised, any uncertainties

about Budesonide prolonged-release capsules (missing information), and how more information will be obtained about the important risks and uncertainties.

There are no safety concerns associated with use of Budesonide prolonged-release capsules.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Budesonide prolonged-release capsules are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

A RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Budesonide prolonged-release capsules
A Marketing Authorisation for Budesonide prolonged-release capsules was granted in the UK on 10 January 2022.

The full PAR for Budesonide prolonged-release capsules follows this summary.

This summary was last updated in March 2022.

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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 Budesonide 3 mg prolonged-release capsules (PL 47026/0006) could be approved.

The product is approved for the following indications:

- Crohn's disease - Induction of remission in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon.

- Microscopic colitis - Induction of remission in patients with active microscopic colitis. Maintenance of remission in patients with microscopic colitis.

The active substance, budesonide, is a glucocorticosteroid with a high local anti-inflammatory effect. The exact mechanism of budesonide in the treatment of Crohn´s disease is not fully understood. Data from clinical pharmacology studies and controlled clinical trials strongly indicate that the mode of action of budesonide is based, at least partly, on a local action in the gut.

This application was approved under Regulation 52B of The Human Medicines Regulations 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be a hybrid medicinal product of a suitable originator product, Entocort CR 3 mg Capsules, that has been licensed within the United Kingdom (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 is for a hybrid medicinal product of a suitable reference product.

Data from two bioequivalent studies were submitted with this application. These 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 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 UK on 10 January 2022.

II QUALITY ASPECTS

II.1 Introduction

This product contains 3 mg of budesonide in each prolonged-release capsule.

In addition to budesonide, this product also contain the excipients sugar spheres (maize starch and sucrose), ethylcellulose, polysorbate 80, methacrylic acid-methyl methacrylate copolymer (1:1) and triethyl citrate, and talc in the capsule fill. The capsule shell contains black iron oxide (E172), red iron oxide (E172), titanium dioxide (E171) and gelatin.

The finished product is packaged in high density polyethylene (HDPE) bottles, in pack sizes of 20, 45, 50, 60, 90 or 100 prolonged-release capsules. 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.

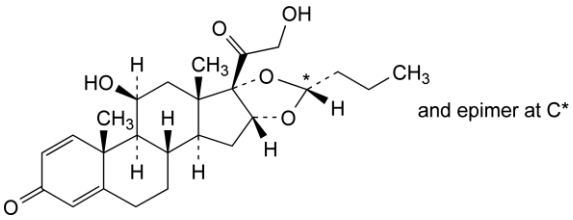
II.2 ACTIVE SUBSTANCE

rINN: Budesonide

Chemical Name: Mixture of the C-22*S* (epimer A) and the C-22*R* (epimer B) epimers of 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione

Molecular Formula: $C_{25}H_{34}O_6$

Chemical Structure:



Molecular Weight: 430.5 g/mol

Appearance: White or almost white, crystalline powder

Solubility: Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96 per cent).

Budesonide 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.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution 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.

With the exception of gelatin, no excipients of animal or human origin are used in the final product. EDQM certificates have been provided for gelatin.

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 2 years, with the storage conditions 'This medicinal product does not require any special temperature storage conditions' and 'Store in the original container in order to protect from light/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
As the pharmacodynamic, pharmacokinetic and toxicological properties of budesonide are well-known, no new non-clinical studies are 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 this application.

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

III.4 Toxicology
No new toxicology data were provided 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 this is a hybrid application of an already authorised product, it is not expected that environmental exposure will increase 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
In accordance with the regulatory requirements, data from two bioequivalence studies have been submitted with this application. This study were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence studies.

Bioequivalence study 1 (single-dose, replicate design, fasting conditions)

This study was an open label, randomised, two-treatment, three-period, three-sequence, single-dose, replicate, crossover oral bioequivalence study comparing the test product Budesonide Enteric coated capsules 3 mg versus the reference product Entocord Modified Release Capsules 3 mg, in normal healthy, adult male and female human subjects under fasting conditions.

Subjects were administered a single oral dose (1 x 3 mg capsule) of either the test (T) or reference product (R) with 240 ml of water, following an overnight fast of at least 10 hours. Blood samples were taken pre-dose and up to 48 hours post dose, with a washout period of seven days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 01 (B): Geometric Means, Ratios and 90% Confidence Interval for Budesonide (N=74):

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval for log transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
C_{max}	836.0658	829.2895	100.8171	95.5087	106.4206
AUC_{0-t}	8152.5353	7898.8675	103.2114	99.1603	107.4281
AUC_{0-inf}	8408.8148	8178.7654	102.8128	98.8500	106.9343
AUC_{0-4}	809.1518	910.6747	88.8519	72.9612	108.2035
AUC_{4-t}	7063.3942	6604.2269	106.9526	102.1074	112.0278
AUC_{0-12}	5116.4598	4995.1174	102.4292	98.0572	106.9962
AUC_{12-t}	2805.8770	2720.3812	103.1428	96.4382	110.3135

*Geometric mean was taken as the antilog (exponential) of the least square mean of the log transformed data.

The replicate design was chosen because high variability (>30%) of C_{max} was observed in previous studies for budesonide. The intra-subject variability of the reference product for the log-transformed pharmacokinetic parameters AUC_{0-4} were found to be >50%; hence the acceptance limits for AUC_{0-4} were widened up to 69.84% – 143.19%.

According to 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 products, under fasted conditions.

Bioequivalence study 2 (single-dose, replicate design, fed conditions)

This study was an open label, randomised, two-treatment, three-period, three-sequence, single-dose, replicate, crossover oral bioequivalence study comparing the test product Budesonide Enteric coated capsules 3 mg versus the reference product, Entocord modified release capsules 3 mg in normal healthy, adult male and female human subjects under fed conditions.

After an overnight 10-hour fast, subjects were administered a single dose (1 x 3 mg capsule) of either the test (T) or reference (R) product with 240 ml of water under fed conditions (30 minutes after the intake of a standard high-fat high-calorie breakfast). Blood samples

were taken pre-dose and up to 48 hours post dose, with a washout period of 10 days between treatment Periods I and II and seven days between treatment Periods II and III.

A summary of the pharmacokinetic results is presented below:

Table 2: Geometric means, Ratios and 90% Confidence Interval for Budesonide (N =68)

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval for log transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
Cmax	**1487.9844**	**1602.6328**	**92.8462**	**87.0875**	**98.9858**
AUC_{0-t}	**10101.9611**	**10995.9827**	**91.8696**	**87.6652**	**96.2756**
AUC_{0-inf}	10398.7457	11282.8398	92.1643	88.0195	96.5042
AUC_{0-6}	1383.3600	1879.1645	73.6157	63.4007	85.4766
AUC_{6-t}	8041.1377	8444.9988	95.2177	90.0683	100.6616
AUC_{0-12}	6611.1477	7451.0849	88.7273	83.8021	93.9420
AUC_{12-t}	3120.1056	3236.6162	96.4002	89.8263	103.4553

* Geometric mean was taken as the antilog (exponential) of the Least square mean of the ln-transformed data

The replicate design was chosen because high variability (>30%) of C_{max} was observed in previous studies for budesonide. The intra-subject variability of the reference product for the log-transformed pharmacokinetic parameters AUC_{0-6} and AUC_{12-t} were found to be >50% and>30, respectively; hence the acceptance limits for AUC_{0-6} and AUC_{12-t} were widened up to 69.84% - 143.19% and 79.64% -125.57%, respectively.

The Test/Reference ratios and their 90% confidence intervals for the parameters C_{max}, AUC_{0-t}, AUC_{0-inf}, AUC_{6-t} and $AUC_{0-12.}$ were within the specified limits for bioequivalence acceptance, but the calculated confidence intervals for AUC_{0-6} (69.84% - 143.19%) failed to show bioequivalence between the test and reference products. However, as the intra-subject variability of the reference product for AUC_{0-6} was found to be >50% and the additionally analysed parameter AUC_{0-12} (which includes AUC_{0-6}) demonstrated bioequivalence, it is concluded that bioequivalence has been demonstrated between the test product and the reference product under fed conditions.

Overall Conclusion on Bioequivalence

As the reference product Entocord modified release capsules 3 mg used in the bioequivalence studies are considered to be equivalent to the UK reference product, bioequivalence has also been shown between the test product and the UK reference product, Entocort CR 3 mg Capsules, under fed and fasting conditions.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data have been submitted for this application and none were required.

IV.5 Clinical safety

With the exception of the safety data from the clinical studies submitted with this application, no new safety data were submitted. The safety data submitted showed that the product was well-tolerated. No new or unexpected safety issues were raised from these data.

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 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.

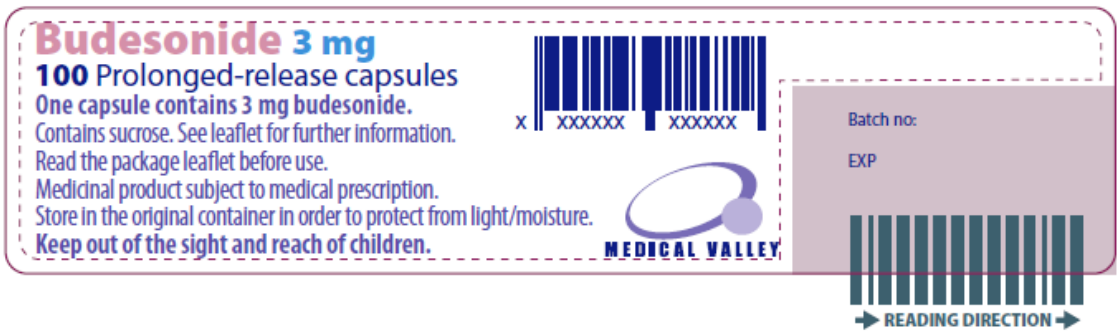
Extensive clinical experience with budesonide is considered to have demonstrated the therapeutic value of the product.

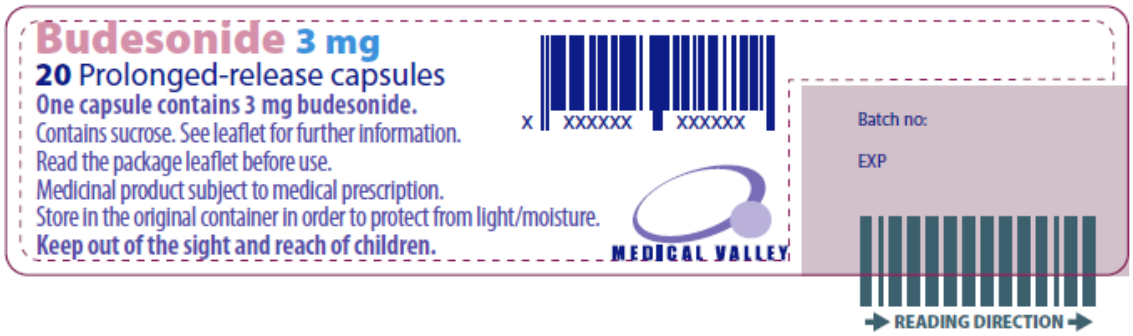
The benefit/risk is, therefore, considered to be positive.

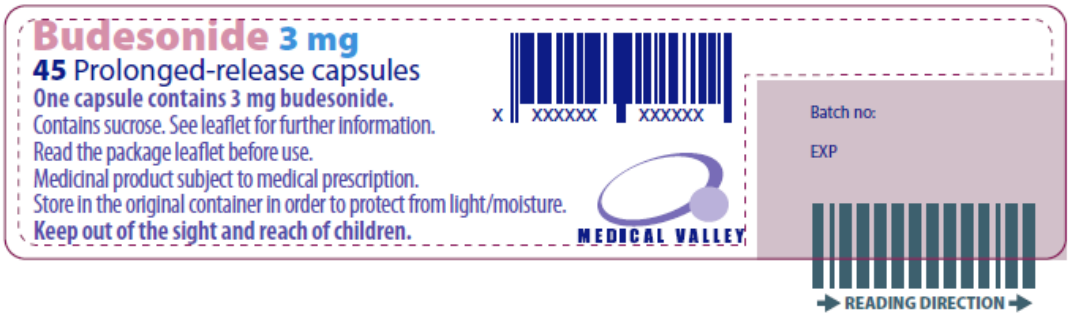
The Summary of Product Characteristics (SmPC), PIL and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved versions of the SmPC and PIL for these products are available on the MHRA website.

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


Budesonide 3 mg
100 Prolonged-release capsules
One capsule contains 3 mg budesonide.
Contains sucrose. See leaflet for further information.
Read the package leaflet before use.
Medicinal product subject to medical prescription.
Store in the original container in order to protect from light/moisture.
Keep out of the sight and reach of children.
x XXXXXX XXXXXX
MEDICAL VALLEY
Batch no:
EXP
READING DIRECTION


Budesonide 3 mg
20 Prolonged-release capsules
One capsule contains 3 mg budesonide.
Contains sucrose. See leaflet for further information.
Read the package leaflet before use.
Medicinal product subject to medical prescription.
Store in the original container in order to protect from light/moisture.
Keep out of the sight and reach of children.
x XXXXXX XXXXXX
MEDICAL VALLEY
Batch no:
EXP
READING DIRECTION


Budesonide 3 mg
45 Prolonged-release capsules
One capsule contains 3 mg budesonide.
Contains sucrose. See leaflet for further information.
Read the package leaflet before use.
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Keep out of the sight and reach of children.
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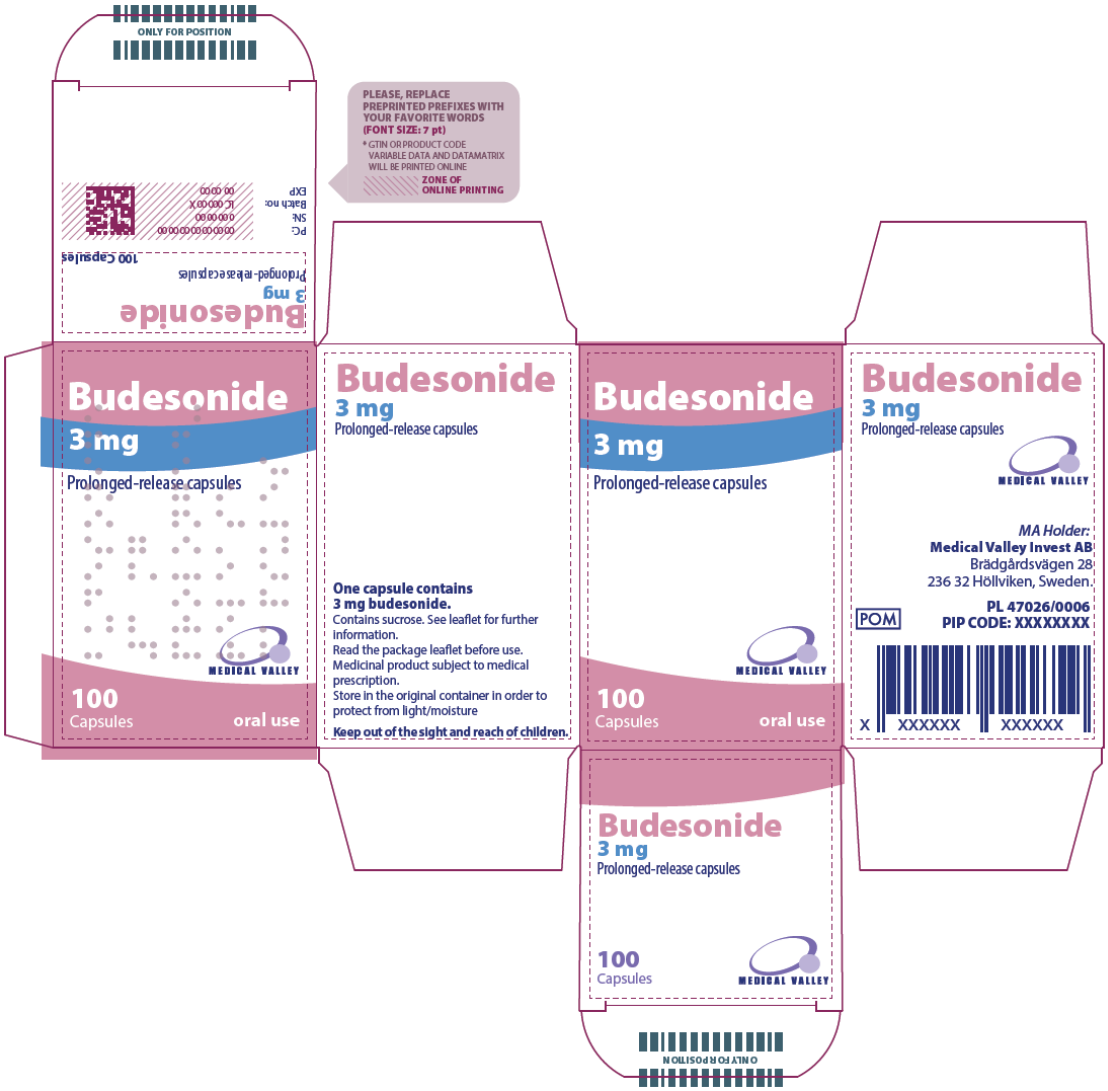
ONLY FOR POSITION
PLEASE, REPLACE PREPRINTED PREFIXES WITH YOUR FAVORITE WORDS (FONT SIZE: 7 pt)
* GTIN OR PRODUCT CODE VARIABLE DATA AND DATAMATRIX WILL BE PRINTED ONLINE
ZONE OF ONLINE PRINTING
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3 mg
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MEDICAL VALLEY
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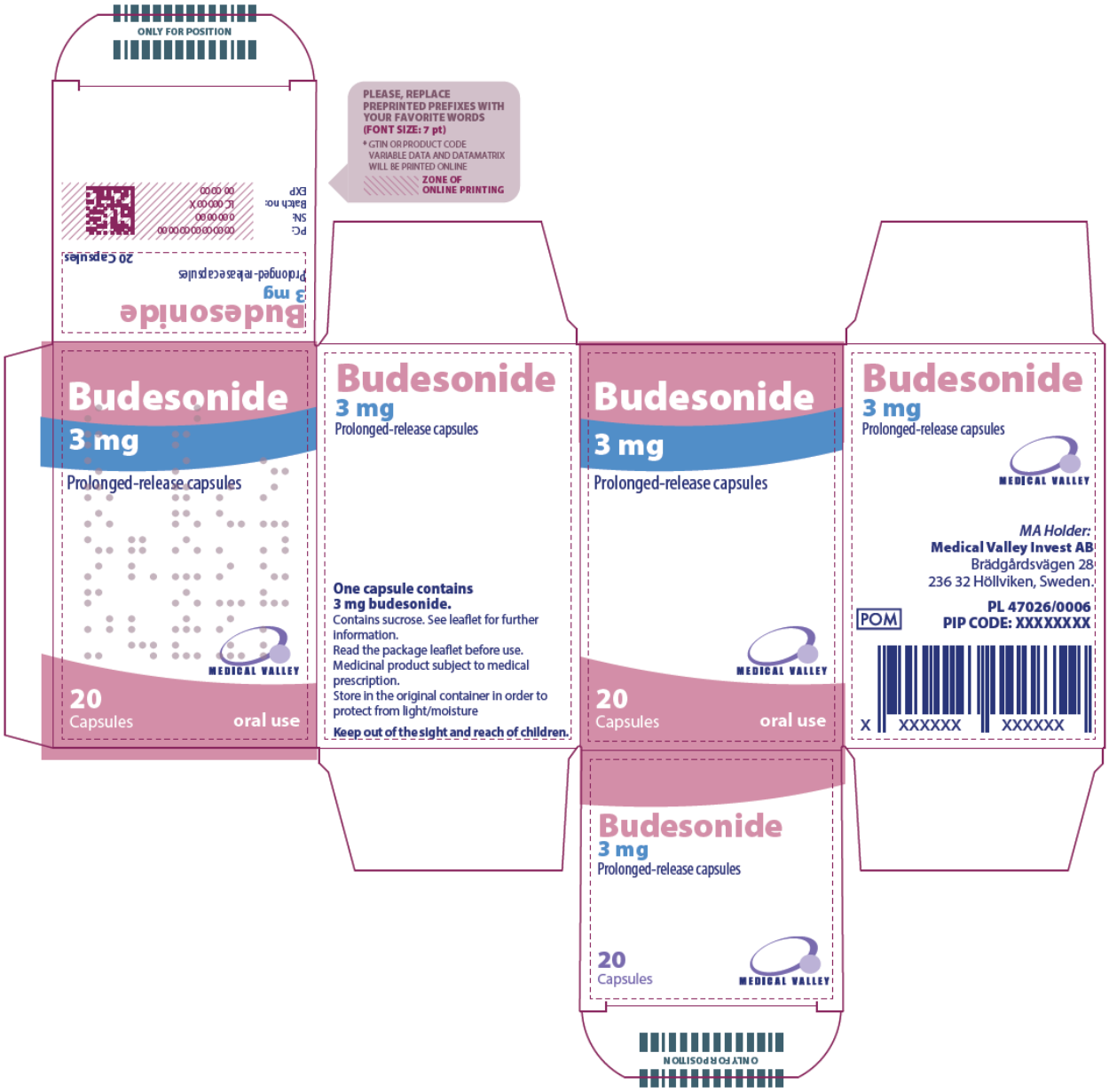
MA Holder:
Medical Valley Invest AB
Brädgårdsvägen 28
236 32 Höllviken, Sweden.
POM
PL 47026/0006
PIP CODE: XXXXXXXX
X XXXXXX XXXXXX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Batch no:
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PIP CODE: XXXXXXXX
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Budesonide
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Capsules
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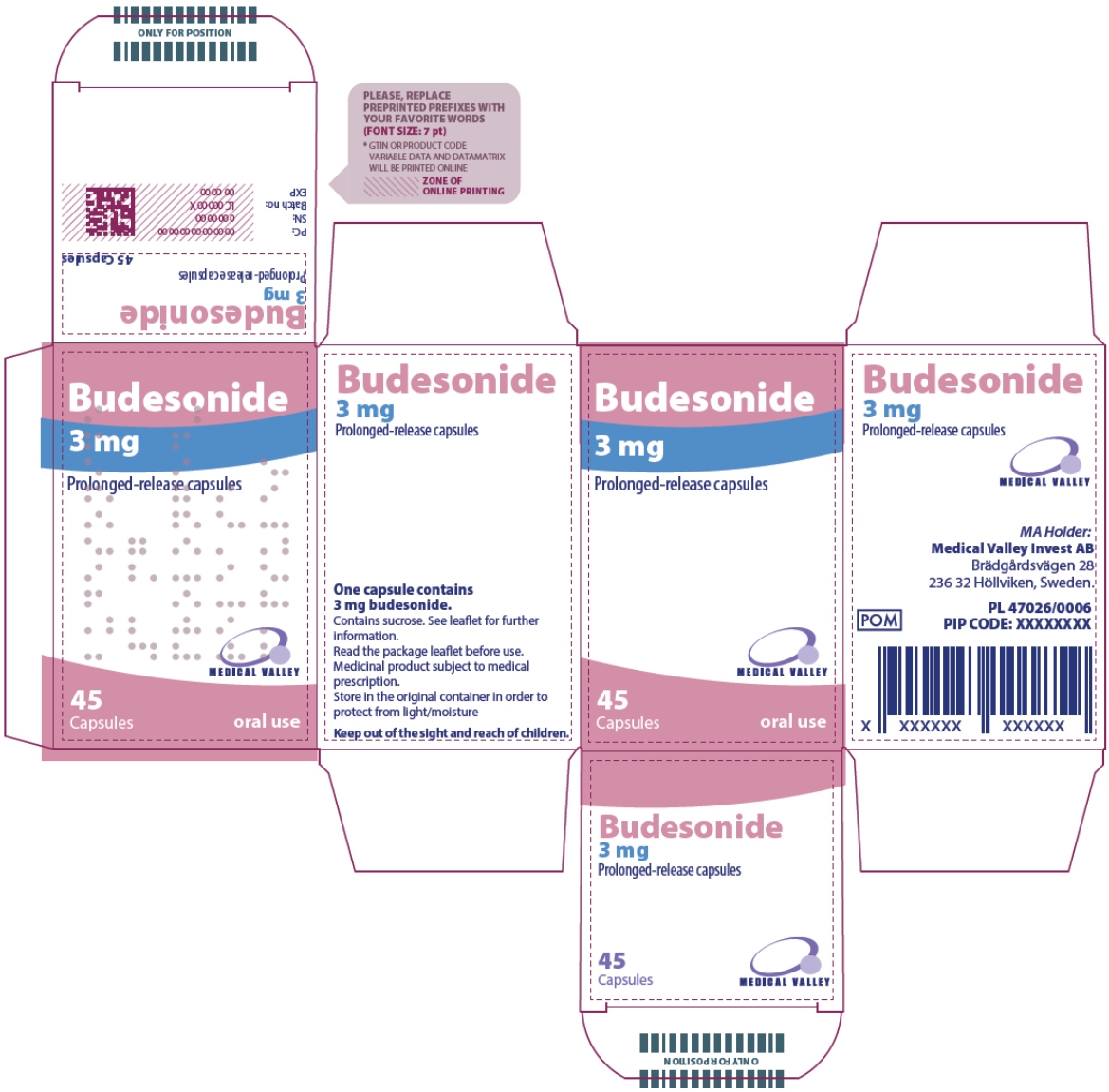
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236 32 Höllviken, Sweden.
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PL 47026/0006
PIP CODE: XXXXXXXX
X XXXXXX XXXXXX
Budesonide
3 mg
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45
Capsules
MEDICAL VALLEY
ONLY FOR POSITION

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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 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**