Proposed packaging material		
Code	Pulmicort Respules 0.25 mg & 0.5 mg (20s) OI-PI-01.01	
Submission	☐NDA ☐Renewal ☒Variation change detail no.: MU-136482-165336, MU-136482-165337	
Code of previous version	N/A	
Changes	Additional North Ryde as Alternative Manufacturing Site	
Reference	☐CDS version: ☐CPIL version:	☐SmPC country/version/date: ☐GRL approval:
Name & Date	INS (21-Feb-2023)	

PULMICORT®

(budesonide for oral inhalation)

Sterile

PRODUCT INFORMATION

QUALITATIVE & QUANTITATIVE COMPOSITION

One single dose unit contains 0.5 mg or 1.0 mg budesonide per 2 mL.

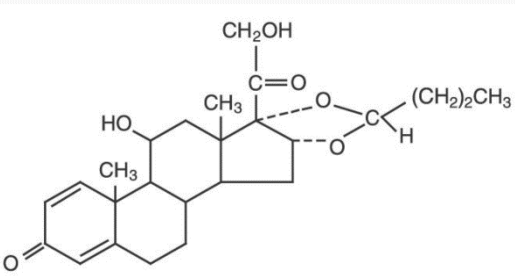
For excipients, see section LIST OF EXCIPIENTS.

PHARMACEUTICAL FORM

Sterile nebuliser suspension. White to off-white suspension in plastic single dose units.

NAME OF THE DRUG

The active ingredient, budesonide, is a non-halogenated glucocorticoid structurally related to 16α hydroxyprednisolone. The chemical name is 16α, 17α - 22R, S-propylmethylenedioxy-pregna-1, 4-diene-11β, 21-diol-3, 20-dione; MW 430.5.



CAS Number: 51333-22-3

DESCRIPTION

Budesonide is a white to off-white powder, freely soluble in chloroform, sparingly soluble in ethanol and practically insoluble in water and heptane. Budesonide melts with decomposition

between 224°C and 231.5°C.

PULMICORT RESPULES nebulising suspension for inhalation is a white to off-white suspension in plastic single dose units. PULMICORT RESPULES contain budesonide 0.5mg/2 mL or 1.0 mg/2 mL as the active ingredient plus, disodium edetate, sodium chloride, polysorbate 80 (E433) citric acid – anhydrous (E330), sodium citrate (E331) and water for injections.

PHARMACOLOGY

Pharmacotherapeutic group: Inhalation drugs for obstructive airway diseases.ATC-code R03B A02

PULMICORT is a corticosteroid for inhalation use in the treatment and prophylaxis of asthma.

Studies in animals and humans have shown an advantageous ratio between topical anti-inflammatory activity and systemic glucocorticoid effect over a wide dose range. This is explained by the extensive first pass hepatic degradation of budesonide after systemic absorption, approximately 85 – 90%, in combination with the low potency of formed metabolites.

Budesonide is approximately twice as potent as beclomethasone dipropionate as shown inthe skin blanching test for anti-inflammatory activity of topical steroids in humans.
Budesonide has, however, less systemic effect than beclomethasone dipropionate, as measured by depression of morning plasma cortisol and effect on differential WBC count. The improved ratio of topical anti-inflammatory activity to systemic effect of budesonide is due to high glucocorticoid receptor affinity combined with a high first pass metabolism and ashort half-life.

Doses of 0.8 mg have been found to suppress plasma cortisol levels and urinary cortisol secretion. A single inhalation of 3.2 mg budesonide was found to suppress plasma cortisol levels to a degree similar to 10 mg oral prednisolone.

Budesonide has been shown to counteract the mainly "IgE" but not the mainly "IgG" mediated lung anaphylaxis in guinea pigs. Pre-treatment for one to four weeks with inhaledbudesonide 1 mg daily in asthmatic patients inhibited the immediate bronchial reaction to allergen challenge in a time-related manner; the late reaction is inhibited after one week of inhaled treatment.

Inhaled budesonide pre-treatment for 2 to 4 weeks has also been shown to reduce non-specific bronchial hyper-responsiveness in asthmatic patients to both direct (histamine, methacholine) and indirect (exercise) provocative stimuli in a time-related manner.

Budesonide did not potentiate ß-receptor-mediated bronchodilation and did not affect theophylline-induced relaxation of respiratory airway smooth muscle in guinea pigs. In man, single oral inhalations of up to 1.6 mg budesonide produced mild bronchodilation. This effect is maximal at 6 hours after inhalation with a duration of 12 hours.

Clinical – croup

A number of studies in children with croup have compared Pulmicort Respules with placebo. Examples of representative studies evaluating the use of Pulmicort Respules for the treatment of children with croup are given below.

Efficacy in children with mild to moderate croup

A randomised, double-blind placebo-controlled trial in 87 children (aged 7 months to 9 years), admitted to hospital with a clinical diagnosis of croup, was conducted to determine whether Pulmicort Respules improves croup symptom scores or shortens the duration of stay in hospital. An initial dose of Pulmicort Respules (2 mg) or placebo was given followed by either Pulmicort Respules 1 mg or placebo every 12 hours. Pulmicort Respules statistically significantly improved croup score at 12 and 24 hours and at 2 hours in patients with an initial croup symptom score above 3. There was also a 33% reduction in the length of stay.

Efficacy in children with moderate to severe croup

A randomised, double-blind, placebo-controlled study compared the efficacy of Pulmicort Respules and placebo in the treatment of croup in 83 infants and children (aged 6 months to8 years) admitted to hospital for croup. Patients received either Pulmicort Respules 2 mg or placebo every 12 h for a maximum of 36 h or until discharge from hospital. The total croup symptom score was assessed at 0, 2, 6, 12, 24, 36 and 48 hours after the initial dose. At 2 hours, both the Pulmicort Respules and placebo groups showed a similar improvement in

croup symptom score, with no statistically significant difference between the groups. By 6 hours, the croup symptom score in the Pulmicort Respules group was statistically significantly improved compared with the placebo group, and this improvement versusplacebo was similarly evident at 12 and 24 hours.

Acute Exacerbations of Asthma

Evidence from the 10 key paediatric studies showed that a daily dose nebulised budesonide dose of 1.5 mg to 4 mg is effective. All doses investigated in the key paediatric studies, either as a replacement for systemic corticosteroids or in addition to systemic corticosteroids, were consistent with the proposed label, with single doses up to 2 mg and maximum daily doses of 4 mg. Daily doses up to 6 mg may be considered in children aged 5 years or over. The use of this higher dose of nebulised budesonide in paediatric patients is supported by efficacy and safety data from AstraZeneca-sponsored Study 04-9305. The safety data in these studies were consistent with the know safety profile of budesonide in patients with asthma, therefore there was no evidence of additional safety concerns due to short-term use at an elevated dose.

In the clinical studies supporting the efficacy and safety of nebulised budesonide to treat acute exacerbations of asthma, duration of nebulised budesonide treatment was typically either less than 1 day or up to 3-5 days, although some studies had longer duration. A 10- day limit for treatment of exacerbations in paediatric and adult patients is proposed to provide appropriate treatment duration for acute exacerbations of asthma at the appropriate nebulised budesonide doses. Nebulised budesonide is indicated for the treatment of bronchial asthma with approved posology for maintenance treatment, and treatment can therefore continue beyond 10 days at these lower doses.

Key adult study Sun *et al* 2012 investigated total daily doses of 2 mg (1 mg BID), 4 mg (2 mg BID) and 8 mg (2 mg four times daily) in adult patients with severe acute exacerbations of asthma. In this study, a total daily dose of 8 mg was as effective as systemic corticosteroids (intravenous methylprednisolone 40 mg once daily) at all time points assessed, while total daily dose of 4 mg was as effective as systemic corticosteroids from 72 hours after the start of treatment. Treatment with systemic corticosteroids in this study resulted in decreases inmean cortisol concentrations and increases in mean blood glucose Concentrations, whichwere not reported with budesonide treatment. The results for the 8 mg daily dose of nebulised budesonide support the inclusion of this dose in the proposed label for similar efficacy to systemic corticosteroids with a better safety profile. A total daily dose of 20 mg (five 4 mg doses in 24 hours) was investigated in the key efficacy study in adult patients (Study 04-3022), dosing was therefore consistent with the maximum single dose proposed for the treatment of acute

exacerbations of asthma in adults, although the total daily dose was higher. In this study, treatment with nebulised budesonide led to improvements in lung function in patients with asthma exacerbations. These improvements were comparable to those in patients receiving a high dose of systemic corticosteroid used (160 mg prednisolone, as well as a lower 30 mg dose). Crucially, there was no evidence of additional safety concerns due to short-term use of elevated doses of nebulised budesonide in this study.

Daily nebulised budesonide doses between 4 mg and 8 mg have also been shown to be efficacious and well-tolerated in the management of exacerbations of chronic obstructive pulmonary disease.

Following are other new supporting data for AE Asthma:

Study by Bahrami et al. (2020) on subjects aged 2-12 years old with acute asthma (n=80) that treated with budesonide or placebo, and standard therapy (oxygen, beta-2 agonist, hydrocortisone), showed subjects without symptoms after 48 hours in percentage as follows:

- Wheezing score: 95% vs. 17,5% (p<0,001)
- Cough score: 100% vs. 10% (p<0,001)
- Distress score: 100% vs. 87,5% (p=0,021)

Study by Abood et al. (2021) on subject aged 1-12 years old with mild to moderate exacerbation asthma (n=100 that treated with budesonide + salbutamol or salbutamol showed:

- The decrease of pulmonary index score after 30 minutes: 35,9% vs 22,1% (p=0,001)
- Duration of emergency department stay (minutes): 63,30±21,71 vs. 77,40±16,13 (p=0,001)

Local study by Susanti et al. (2002) on subjects aged 12-65 years old with severe acute asthma (n=64) that treated with budesonide + terbutaline or metilprednisolon + terbutaline showed:

- Wheezing improvement: 81.3% vs. 62.5%
- Improvements in peak expiratory flow (APE) 120 min: 66.9 ± 18.2% vs. 64.8 ± 18.8%
- Reported side effects are palpitations and dryness in the mouth, with the highest percentage at minute 60 is 68.8% vs. 75%, p>0.05; and 59.4% vs. 21.9%, p<0.005, respectively.

Exacerbations of COPD

Several studies on nebulised budesonide, 4-8 mg/day has shown to effectively treat exacerbations of COPD. The efficacy of Budesonide was evaluated in an open label, randomised, comparative study in 78 hospitalised patients with acute exacerbations of COPD in two parallel groups receiving nebulised budesonide(n=37) 4 mg/day (2 mg twice daily) or intravenous infusion of prednisolone 120–180 mg/day (n=41) for 7-14 days. Patients treated with nebulized budesonide or prednisolone showed similar improvements in FEV1, SpO2 (saturation as measured by pulse oximetry) and symptoms (CAT score).

In a multi-center randomised controlled, single-blind study involving 410 patients with acute exacerbations of COPD, patients were treated with nebulised budesonide 6 mg/day (2 mg three times/day); or intravenously injected methylprednisolone (40 mg/day) for 10 days.
Clinical efficacy of nebulised budesonide in comparison to systemic methylprednisolone as measured by FEV1, PaCo2 and symptoms (CAT score) was comparable, while PaO2 improved more in the methylprednisolone group. In a double-blind randomised placebo-controlled study involving 199 patients with acute exacerbations of COPD, patients were treated with nebulised budesonide 8 mg/day (2 mg four times a day (n=71) or 30 mg oral prednisolone every 12 hours (n-62) or placebo (n=66) for 3 days. Improvement in post bronchodilator FEV1 compared to placebo was 0.10 L for budesonide and 0.16 L for prednisolone; the difference between the active treatments was not statistically significant. The proportion of patients showing clinical improvement in postbronchodilator FEV1 of at least 0.15 L was greater in the nebulised budesonide group (34%) and the prednisolone group (48%) than in the placebo group (18%). The differences were statistically significant for both active treatments versus placebo ($p < 0.05$) but not between the active treatments.

Addition of indication for treatment of exacerbating chronic obstructive pulmonary disease (COPD) is also supported by study conducted by Zhang et al. (2020) with randomized design in subjects with acute exacerbation of chronic obstructive pulmonary disease (n=321) treated with budesonide with dose of 4mg/day (1 mg Q6h) or 8 mg/day (2 mg Q6h) or 8 mg/day (4 mg Q12h), showed improvement based on observation at 5 days after therapy, as follows:

- PaO2 (mmHg): 72.1 ± 10.7 vs. 74.7 ± 14.8 vs. 76.2 ± 16.3
- CAT score: 9.5 ± 3.3 vs. 9.0 ± 4.7 vs. 8.2±3.2
- FEV1% predicted: 58.6 ± 8.3 vs. 57.3 ± 8.5 vs. 61.7 ± 8.1

Pharmacokinetics

Approximately 10% of the discharged dose of PULMICORT aerosol is deposited in the lungs.

The volume of distribution of budesonide in adult man is approximately 300 L and in children is 3.1 to 4.8 L/kg indicating a high tissue affinity. Plasma protein binding is 88.3 ± 1.5% in humans.

In adults the plasma half-life following inhalation via aerosol was 2.0 ± 0.2 hours and inchildren 1.5 hour with peak plasma levels occurring immediately after administration.

Negligible biotransformation was observed in human lung and serum preparations.

PULMICORT is 90% inactivated on first pass through the liver, via metabolism to more polar metabolites with a more than 100-fold lower glucocorticosteroid systemic activity than the parent compound.

In human volunteers who inhaled tritiated budesonide, 31.8 ± 7.5% of the discharged dose was recovered in urine and 15.1 ± 4.3% in faeces (0 – 96 h). Plasma clearance of unchanged budesonide was calculated to be 84 L/h in adults and 1.5 to 2 L/h/kg in children.

THERAPEUTIC INDICATIONS

Pulmicort nebuliser suspension is indicated in patients with:

- Treatment of bronchial asthma.
- Treatment of moderate to severe acute laryngotracheobronchitis (croup) in infants and children.
- Treatment of acute exacerbations asthma.
- Treatment of exacerbations of chronic obstructive pulmonary disease (COPD).

CONTRAINDICATIONS

Hypersensitivity to budesonide or any other ingredients.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Bronchospasm

PULMICORT is not indicated for rapid relief of bronchospasm. PULMICORT is therefore not suitable as sole therapy for the treatment of status asthmaticus or other acute exacerbations of asthma where intensive measures are required.

If patients find short-acting bronchodilator treatment ineffective, or they need more inhalations than usual, medical attention must be sought. This indicates a worsening of theunderlying conditions and warrants a reassessment of the therapy.

Oral corticosteroid usage

Particular care is needed in patients who are being transferred from oral corticosteroids to PULMICORT, since they may remain at risk of impaired adrenal function for some considerable time (see SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE — Potential systemic effect of inhaled corticosteroids: HPA axis suppression and adrenal insufficiency). These patients should be instructed to carry an appropriate warning card (see Clinical Management: Patients — Oral corticosteroid dependent).

Patients previously receiving high doses of systemic steroids may regain earlier allergic symptoms such as rhinitis and eczema when transferred from oral therapy to PULMICORT due to the reduced systemic steroid effect of budesonide (see Clinical Management: Patients – Oral corticosteroid dependent).

Potential systemic effects of inhaled corticosteroids

Inhaled steroids are designed to direct glucocorticoid delivery to the lungs in order to reduce overall systemic glucocorticoid exposure and side effects. However inhaled steroids may have adverse effects; possible systemic effects of inhaled steroids include depression of the HPA axis, reduction of bone density, cataracts and glaucoma and retardation of growth rate in children. In steroid-dependant patients, prior systemic steroid usage may be a contributing factor (see SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE - Oral corticosteroid usage), but such effects may occur amongst patients who use only inhaled steroids regularly.

<u>HPA axis suppression and adrenal insufficiency</u>

Dose-dependant HPA axis suppression (as indicated by 24 hour urinary and/or plasma cortisol

AUC) has been observed with inhaled budesonide, although the physiological circadian rhythms of plasma cortisol were preserved. This indicates that the HPA axis suppression may represent a physiological adaption in response to inhaled budesonide, notnecessarily adrenal insufficiency. The lowest dose that results in clinically relevant adrenal insufficiency has not been established. Very rare cases of clinically relevant adrenal dysfunction have been reported in patients using inhaled budesonide at recommended doses.

Particular care is needed in patients who are being transferred from oral corticosteroids to PULMICORT, since they may remain at risk of impaired adrenal function for some considerable time (see SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE - Oral corticosteroid usage). Patients who have required high dose emergency corticosteroid therapy, prolonged treatment at the highest recommended dose of inhaled corticosteroids or patients administering concomitant medication metabolised by CYP3A4 (see INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION) may also be at risk. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress such as trauma, surgery, infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Monitoring for signs of adrenal dysfunction is advisable in these patient groups. For these patients additional systemic glucocorticosteroid cover should be considered during periods of stress, severe asthma attack or elective surgery.

Bone density

Whilst corticosteroids may have an effect on bone mass at high doses, long term follow up (3 – 6 years) studies of budesonide treatment in adults at recommended doses, have not demonstrated a negative effect on bone mass compared to placebo, including one study conducted in patients with a high risk of osteoporosis. The lowest dose that does effect bone mass has not been established.

Bone mineral density measurements in children should be interpreted with caution as an increase in bone area in growing children may reflect an increase in bone volume. In three large medium to long term (12 months – 6 years) studies in children (5 – 16 years), no effects on bone mineral density were observed after treatment with PULMICORT (189 – 1322 µg/day) compared to nedocromil, placebo or age matched controls. However, in a randomised

18 month study (n=176; 5 – 10 years), bone mineral density was significantly decreased by 0.11 g/cm^2 (p=0.023) in the group treated with inhaled budesonide via Turbuhaler compared with the group treated with inhaled disodium cromoglycate. The doseof budesonide was 400 µg twice daily for 1 month, 200 µg twice daily for 5 months and 100
µg twice daily for 12 months and the dose of disodium cromoglicate 10 mg three times daily. The clinical significance of this result remains uncertain. Should not be used as a long term treatment in children.

Growth

Long term studies show that children treated with inhaled budesonide ultimately achieve adult target height. However, an initial reduction of growth velocity (approximately 1 cm) hasbeen observed and is generally within the first year of treatment. Rare individuals may be exceptionally sensitive to inhaled corticosteroids. Height measurements should be performed to identify patients with increased sensitivity. The potential growth effects of prolonged treatment should be weighed against the clinical benefit. To minimise the systemic effects of inhaled corticosteroids, each patient should be titrated to his/her lowesteffective dose (see POSOLOGY AND METHOD OF ADMINISTRATION).

Infections and tuberculosis

High doses of glucocorticosteroids may mask some signs of existing infection and new infections may appear during their use. Special care is needed in patients with active or quiescent pulmonary tuberculosis or fungal, bacterial or viral infections of the respiratory system.

Hepatic function

Decreased liver function may affect the ability to eliminate budesonide. This may be clinically relevant in patients with severely compromised liver function.

Positive pressure delivery systems

Respiratory drugs should not be used with positive pressure delivery systems (e.g. IPPB) in pulmonary conditions involving pneumothorax, air cysts or mediastinal emphysema unless special drainage is performed.

Carcinogenicity and mutagenicity

The carcinogenic potential of budesonide has been evaluated in mouse and rat at oral doses up to 200 and 50 µg/kg/day, respectively. No oncogenic effect was noted in the mouse. One study indicated an increased incidence of brain gliomas in male Sprague-Dawley rats given budesonide, however the results were considered equivocal. Further studies performed in male Sprague-Dawley and Fischer rats showed that the incidence of gliomas in the budesonide-treated rats was low and did not differ from that in the reference glucocorticoid groups or the controls. It has been concluded that treatment with budesonide does not increase the incidence of brain tumours in the rat.

In male rats dosed with 10, 25 and 50 µg/kg/day, those receiving 25 and 50 µg/kg/day showed an increased incidence of primary hepatocellular tumours. This was observed in all three steroid groups (budesonide, prednisolone, triamcinolone acetonide) in a repeat study inmale Sprague-Dawley rats thus indicating a class effect of corticosteroids.

The mutagenic potential of budesonide was evaluated in 6 different test systems. Nomutagenic or clastogenic effects of budesonide were found.

USE IN PREGNANCY

In pregnant animals administration of budesonide causes abnormalities of foetal development. The relevance of this finding to man has not been established. Administrationduring pregnancy should be avoided unless there are compelling reasons.

USE IN LACTATION

Budesonide is excreted in breast milk. However, at therapeutic doses of PULMICORT RESPULES no effects on the suckling child are anticipated. PULMICORT RESPULES can be used during breast feeding.

INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION

The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450. Inhibitors of this enzyme e.g. ketoconazole and itraconazole, can therefore increase systemic exposure to budesonide. This is of limited clinical importance for short-term (1-2

weeks) treatment with CYP3A inhibitors, but should be taken into consideration during long-term treatment.

UNDESIRABLE EFFECTS

PULMICORT is generally well tolerated. Most adverse reactions have been mild and of a local character. Systemic effects and oropharyngeal complications caused by budesonide were found to be dose dependent.

Clinical signs of steroid excess were present in 50% of patients (n=10) taking 1.6 mg or more daily of budesonide alone for long periods.

Clinical trials, literature reports and post-marketing experience suggest that the following adverse drug reactions may occur:

Common (more than 1%)

Nose and throat:	hoarseness; sore, mild irritated throat; irritation of the tongue and mouth; dry mouth; oral candidiasis
Respiratory:	cough

Uncommon (less than 1%)

Nose and throat:	irritation of the larynx; bad taste
Gastrointestinal:	diarrhea; nausea
Hypersensitivity reactions:	Immediate and delayed hypersensitivity reactions such as skin reactions (e.g. urticaria, rash, dermatitis), bronchospasm, angioedema and anaphylactic reaction.
Central nervous system:	headache; lightheadedness; thirst; tiredness
Metabolic and nutritional disorders:	weight gain

If oropharyngeal candidiasis develops, it may be treated with appropriate anti-fungal therapy whilst still continuing with PULMICORT therapy. The incidence of candidiasis can generally be held to a minimum by having patients rinse their mouth with water after each inhalation.

In rare cases signs or symptoms of systemic glucocorticosteroid effect, including hypofunction of the adrenal gland and reduction of growth velocity, may occur with inhaled

glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity.

Inhaled steroids may have adverse effects in higher than recommended doses; possible systemic effects of inhaled steroids include depression of the HPA axis, reduction of bone density and retardation of growth rate in children (see SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE — Potential systemic effects of inhaled corticosteroids).

Reduction in growth velocity has been reported in association with administration of inhaled corticosteroids, however studies with budesonide indicate that this is transient and that final adult height may ultimately be achieved (see SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE - Growth).

Dose dependant HPA axis suppression has been observed with budesonide, however this may represent a physiological adaption rather than adrenal insufficiency (see SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE - HPA axis suppression and adrenal insufficiency). The lowest dose that results in clinically relevant adrenal insufficiency has not been established.

No negative effects on bone mass have been observed in adults treated with inhaled budesonide at recommended doses. In children, bone mineral density should be interpreted with caution as an increase in bone area may reflect an increase in bone volume (see SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE - Bone density).

Rare reports of skin bruising have occurred following treatment with inhaled glucocorticosteroids.

Psychiatric symptoms such as behavioural disturbances, nervousness, restlessness and depression have been observed with budesonide as well as other glucocorticosteroids.

Facial skin irritation has occurred in a few cases when a nebuliser with a face mask has been used. To prevent irritation the face should be washed after each use of PULMICORT RESPULES delivered via a nebuliser with a face mask.

Rarely, PULMICORT may provoke bronchoconstriction in hyperreactive patients. Bronchospasm may be treated with an inhaled β2- agonist.

POSOLOGY AND METHOD OF ADMINISTRATION

PULMICORT RESPULES Nebulising Suspension

PULMICORT RESPULES should be administered from a suitable nebuliser. The dose delivered to the patient varies between 40 – 60% of the nominal dose depending on the nebulising equipment used. The nebulisation time and the dose delivered is dependent on flow rate, volume of nebuliser chamber and volume fill. A suitable fill for most nebulisers is 2 – 4 mL.

Some sedimentation may occur during storage of PULMICORT RESPULES. If this does not readily resuspend completely upon shaking, the respules should be discarded.

Bronchial Asthma

Dosage initially, or during periods of severe asthma, or while reducing oral corticosteroids

Adults, Children 12 years and older

1 – 2 mg twice daily

Children age 3 months – 12 years

0.5 – 1 mg twice daily.

Maintenance

The maintenance dose should be individualised and should be the lowest dose, which keeps the patient symptom-free. Recommended doses are:

Adults

0.5 – 1 mg twice daily.

Children age 3 months – 12 years

0.25 – 0.5 mg twice daily.

Acute Laryngotracheobronchitis (Croup)

In infants and children with croup the usual dose is 2 mg of nebulised budesonide given as a single administration of Pulmicort Respules.

Acute Exacerbations of Asthma

Adults

Daily recommended dose is 4 to 8 mg and can be divided into 1 to 4 administrations.

In very severe cases the dose may be further increased. Maximum dose at one occasion should not exceed 4 mg. Treatment with nebulized Pulmicort for acute exacerbations can be continued until clinical improvement, but for no longer than 10 days.

Children (aged 6 months to 17 years)

daily recommended dose is 1.5 to 4 mg, doses up to 6 mg can be considered in children 5 years or above. Daily dose can be divided into 1 to 4 administrations. Maximum dose at one occasion should not exceed 3 mg. Treatment with nebulized Pulmicort for acute exacerbations can be continued until clinical improvement, but for no longer than 10 days.

In both adults and children, nebulised budesonide is not a substitute for systemic corticosteroids in life threatening asthma. Treatment for exacerbations may be followed by ICS (Inhaled Corticosteroids) containing therapy in appropriate doses using suitable delivery systems.

Exacerbations of Chronic Obstructive Pulmonary Disease (COPD)

Patients should be treated with daily doses of 4 to 8 mg of PULMICORT nebulizer suspension, divided into 2 to 4 administrations, until clinical improvement but for no longer than 10 days.

Onset of effect

Following inhaled administration of Pulmicort Nebulizer Suspension for the treatment of exacerbations of COPD the time to symptom improvement is comparable to administration of systemic corticosteroids.

PATIENT INSTRUCTIONS

PULMICORT is not intended for rapid relief of acute episodes of asthma where an inhaled short-acting bronchodilator is required

The patient should be instructed in the proper use of the inhaler device considered appropriate for his/her particular needs. A full set of instructions are provided with each pack of PULMICORT.

In patients in whom aerosol metered dose inhalation technique is incorrect or unamenable to

easy correction, PULMICORT TURBUHALER could be substituted.

Patients also receiving bronchodilators by inhalation should be advised to use the bronchodilator before PULMICORT in order to enhance its penetration into the bronchial tree. Several minutes should elapse between the use of the two inhalers.

Clinical Management

Patients - not oral corticosteroid dependent

Treatment with the recommended doses of PULMICORT usually gives a therapeutic effect within 10 days.

In patients with excessive mucus secretion in the bronchi, an initial short course (about 2 weeks) of an oral corticosteroid, commencing with a high dose and gradually reducing, should be given in addition to PULMICORT.

Patients - oral corticosteroid dependent

Transfer of patients dependent on oral corticosteroids to PULMICORT requires special care because of slow normalisation of the disturbed hypothalamic-pituitary-adrenal function caused by extended treatment with oral corticosteroids (see SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE - Oral Corticosteroid usage and Potential systemic effects of inhaled corticosteroids - HPA axis suppression and adrenal insufficiency).

When PULMICORT treatment is initiated, the patient's asthma should be in a relatively stable phase. The dose of oral corticosteroid should then be reduced gradually to the lowest possible level. The dose of PULMICORT should not be changed while the patient remains on oral corticosteroids.

In many cases, it may be possible to completely replace the oral corticosteroid with inhaled PULMICORT. In other patients, a low oral steroid maintenance dose may be necessary.
Some patients may experience uneasiness during the withdrawal of oral corticosteroids due to the decreased systemic corticosteroid effect. The physician may need to actively support the patient and to stress the reason for the PULMICORT treatment.

The length of time needed for the body to regain sufficient natural corticosteroid production is often extended and may be as long as 12 months. Transferred patients should carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, such as severe infection, trauma or surgery. During such times it may be necessary to give additional oral corticosteroids.

During transfer from oral therapy to PULMICORT, a lower systemic steroid action is experienced. Earlier allergic symptoms may recur (e.g. rhinitis, eczema, conjunctivitis) or patients may suffer from tiredness, headache, muscle and joint pain, lassitude and depression or occasionally nausea and vomiting. In these cases, further medical supportmay be required.

OVERDOSE

Symptoms

In most cases, occasional overdosing will not produce any obvious symptoms but will decrease the plasma cortisol level and increase the number and percentage of circulatingneutrophils. The number and percentage of lymphocytes and eosinophils will decrease concurrently. Habitual overdosing may cause hypercorticism and
hypothalamic-pituitary-adrenal suppression.

Treatment

Withdrawing PULMICORT or decreasing the dose will abolish these effects, although the normalization of the HPA-axis may be a slow process.

LIST OF EXCIPIENTS

Disodium edetate

Sodium chloride

Polysorbate 80

Citric acid, anhydrous

Sodium citrate

Water for Injection

Nitrogen

PRESENTATION

0.5 mg per 2 mL and 1 mg per 2 mL sterile nebulising suspension in single dose polyethylene (plastic)

units.

Packsize

PULMICORT RESPULES 0.25 mg/mL: 4x5 single dose units, Reg. No.: DKI1151302568A1.

PULMICORT RESPULES 0.50 mg/mL: 4x5 single dose units, Reg. No.: DKI1151302568B1.

Storage conditions

Store below 30°C. Do not refrigerate. Unused respules should be discarded three months after opening of foil packs.

HARUS DENGAN RESEP DOKTER

Manufactured by:

AstraZeneca AB

SE-151 85 Södertälje

Sweden

And

AstraZeneca Pty, Ltd

10 -14 Khartoum Road, North Ryde NSW 2113

Australia

Imported by:

PT AstraZeneca Indonesia

Cikarang, Bekasi - Indonesia

Date of Revision

21 February 2023

PULMICORT®

(budesonide for oral inhalation)

Sterile

INSTRUCTION LEAFLET

Before using PULMICORT RESPULES, please read this leaflet and follow the instructions carefully.

IMPORTANT

PULMICORT is not intended for rapid relief of acute episodes of asthma where an inhaled short-acting bronchodilator is required

CAUTION

The content of PULMICORT RESPULES are for inhalation via a nebuliser, and should not be swallowed or injected.

Use only as directed by your physician.

Avoid getting the aerosol in the eyes (we suggest that you use eye goggles).

Wash the face and rinse the mouth out with water after administration of each dose of PULMICORT.

Do not exceed the prescribed dose.

PULMICORT RESPULES can be mixed with 0.9 % saline and with solutions for nebulisation of terbutaline, salbutamol, sodium cromoglycate and ipratropium. The admixture should be used within 30 minutes.

PULMICORT should be added to the nebuliser immediately before use. Medications for nebulisation should not be mixed in advance.

WARNING

Unused, unopened respules should be discarded 3 months after opening of the foil pack. During storage PULMICORT RESPULES should be protected from light by keeping them in the foil envelope.

Instructions for the use of PULMICORT RESPULES

1. Prepare the nebuliser for filling.
2. Detach one PULMICORT RESPULES from the rack by twisting it firmly.
3. Shake the respules.
4. Twist the top off the respules.
5. Squeeze the contents into the reservoir of the nebuliser.

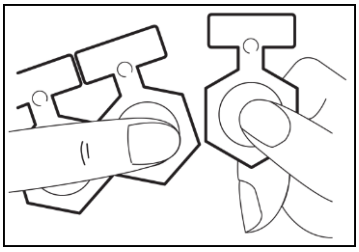
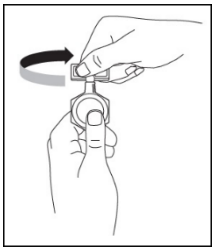
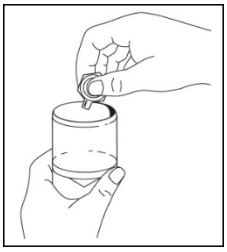
   Do not dilute the contents unless instructed to do so by your physician.

   In some cases, it may be necessary to use only a part of respules content to obtain the prescribed dose.

   Your physician or pharmacist will advise you accordingly.
6. Use the nebuliser as directed, ensuring that the contents of the reservoir are completely used up.
7. After use, clean your nebuliser in accordance with the manufacturer's recommendations.

   Also remember to wash your face and rinse your mouth out with water.

   After each nebulisation, the mouthpiece or facemask should be rinsed in warm water and dried.

Nebulisers and PULMICORT (budesonide) RESPULES

For all solutions used in a nebuliser, it is very important that the mist (aerosol) produced is the right size and strength to work correctly in your lungs.

With PULMICORT RESPULES, this can best be achieved by using a **compressed air jet nebuliser which gives an output of at least 6 to 8 litres per minute.**

A jet nebuliser creates the aerosol mist for you to inhale by using air pumped via an electric compressor or compressed oxygen from a tank.

Please check the instruction manual, or with the manufacturer of your nebuliser to ensure your nebuliser fulfils these requirements.

Please note that it is **not** recommended that an **ultrasonic nebuliser** is used with PULMICORT RESPULES.

An ultrasonic nebuliser creates a high frequency signal to produce vibrations in the liquid and to provide a fog of small droplets which can be inhaled. Use of this type of nebuliser may cause your treatment with PULMICORT RESPULES to be ineffective.

Please also follow the other instructions in this pack.

For further information, please contact your physician, pharmacist or
PT AstraZeneca Indonesia (021) 29979000

Manufactured by: AstraZeneca AB
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And
AstraZeneca Pty, Ltd
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Imported by: PT AstraZeneca Indonesia
Cikarang, Bekasi – Indonesia

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Proposed packaging material		
Code	Pulmicort Respules 0.25 mg & 0.5 mg (20s) OI-PIL-01.01	
Submission	☐NDA ☐Renewal ☒Variation change detail no.: MU-136482-165336, MU-136482-165337	
Code of previous version	N/A	
Changes	Additional North Ryde as Alternative Manufacturing Site	
Reference	☐CDS version: ☐CPIL version:	☐SmPC country/version/date: ☐GRL approval:
Name & Date	INS (21-Feb-2023)	

Informasi Leaflet untuk Pasien

Pulmicort Respules® 0.25 mg/mL dan 0.5 mg/mL, suspensi inhalasi

budesonide

Bacalah leaflet ini secara keseluruhan dengan seksama sebelum Anda menggunakan obat ini karena obat ini mengandung informasi penting untuk Anda

- Simpanlah leaflet ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan berikan obat ini kepada orang lain. Karena ini bisa membahayakan mereka, bahkan jika tanda-tanda penyakit mereka sama dengan Anda.
- Jika Anda mendapatkan efek samping, konsultasikanlah dengan dokter atau apoteker Anda. Ini termasuk kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Lihat bagian 4.

Apa yang ada dalam leaflet ini:

1. Apa itu Pulmicort Respules dan untuk apa obat ini digunakan

Pulmicort Respules digunakan untuk:

- Pengobatan pada asma bronkial.

- Pengobatan untuk laringotrakeobronkitis akut (croup) sedang hingga berat pada bayi dan anak-anak.
- Pengobatan untuk eksaserbasi akut asma.
- Pengobatan untuk eksaserbasi penyakit paru obstrukstif kronis (PPOK).

2. Apa yang perlu Anda ketahui sebelum Anda menggunakan Pulmicort Respules

Jangan gunakan Pulmicort Respules:

- jika Anda alergi terhadap budesonide atau bahan lain dari obat ini (tercantum dalam bagian 6).

Peringatan dan pencegahan:

Bicaralah pada dokter atau apoteker Anda sebelum menggunakan Pulmicort Respules, apabila:

- Anda mengalami infeksi paru-paru.
- Anda memiliki flu atau infeksi dada.
- Anda memiliki masalah pada hati.

Hubungi dokter apabila pandangan Anda kabur atau gangguan pengelihatan lainnya.

Obat-obatan lain dan Pulmicort Respules

Katakan kepada dokter atau apoteker Anda jika Anda baru-baru ini menggunakan obat lain.

Secara khusus, beri tahu dokter atau apoteker Anda jika menggunakan salah satu obat berikut.

- Obat-obatan steroid.
- Obat-obatan HIV (seperti ritonavir atau obat yang mengandung cobicistat).
- Obat-obatan yang digunakan untuk mengobati infeksi jamur seperti ketoconazole.

Obat-obatan ini mungkin dapat dipengaruhi oleh Pulmicort Respules atau dapat mempengaruhi seberapa baik kerjanya. Anda mungkin memerlukan jumlah obat yang berbeda, atau Anda mungkin perlu menggunakan obat-obatan yang berbeda. Dokter atau apoteker Anda akan menyarankan Anda.

Dokter dan apoteker Anda memiliki informasi lebih lanjut tentang obat-obatan untuk berhati-hati atau menghindari saat menggunakan Pulmicort Respules.

Kehamilan, menyusui dan kesuburan

- Jika Anda hamil, atau berencana untuk hamil, bicaralah dengan dokter Anda sebelum menggunakan Pulmicort Respules - jangan gunakan Pulmicort Respules kecuali dokter Anda menyuruh Anda mengkonsumsinya.
- Jika Anda hamil saat menggunakan Pulmicort Respules, jangan berhenti menggunakan Pulmicort Respules tetapi segera hubungi dokter Anda.
- Jika Anda sedang menyusui, bicarakan dengan dokter Anda sebelum menggunakan Pulmicort Respules.

Mengemudi dan menggunakan mesin

Pulmicort Respules tidak menyebabkan efek pada kemampuan Anda mengemudi atau menggunakan alat atau mesin.

3. Bagaimana cara menggunakan Pulmicort Respules

- Selalu gunakan obat ini sesuai petunjuk dokter atau apoteker. Tanyakan kembali pada dokter atau apoteker apabila Anda ragu.
- Larutan dalam Respule harus disimpan dalam nebulizer dan dibuat menjadi kabut halus sebelum dihirup. Hiruplah melalui *face mask* atau *mouthpiece*. Petunjuk penggunaan nebulizer diberikan pada bagian 'Berapa banyak penggunaan'.

  Note: Jangan gunakan nebulizer ultrasonik dengan Pulmicort Respules.
- Asma Anda mungkin membaik dalam waktu 2 hari. Tetapi, untuk mencapai hasil keseluruhan diperlukan waktu sampai dengan 4 minggu. Penting untuk menggunakan Pulmicort Respules setiap hari, walau Anda tidak mengalami gejala asma hari itu.

Berapa banyak penggunaan

Asma

Dokter Anda akan memberi informasi berapa banyak Anda perlu menggunakan, tergantung seberapa parah asma Anda. Dokter mungkin akan menurunkan dosis bila terjadi perbaikan pada asma Anda.

- Dosis rekomendasi pada orang dewasa dan anak-anak di atas 12 tahun adalah 1 mg sampai 2 mg, dua kali sehari.
- Anak-anak di bawah 12 tahun biasanya diresepkan pada dosis rendah, 0.5 mg sampai 1 mg, dua kali sehari.

Laringotrakeobronkitis Akut (Croup)

Pada bayi dan anak-anak dengan croup, dosis normal adalah 2 mg budesonide yang dinebulisasi dalam satu kali pemberian Pulmicort Respules.

Eksaserbasi Akut Asma

Dewasa

Dosis harian yang direkomendasikan adalah 4 sampai 8 mg dan dapat dibagi menjadi 1 hingga 4 administrasi. Pada kasus sangat parah dosis dapat ditambahkan. Dosis maksimum dalam satu kali pemberian tidak boleh lebih dari 4 mg. Pengobatan dengan Pulmicort Respules untuk eksaserbasi akut dapat dilanjutkan sampai perbaikan klinis, namun tidak lebih dari 10 hari.

Children (usia 6 bulan hingga 17 tahun)

Rekomendasi dosis hariam 1.5 hingga 4 mg, dosis hingga 6 mg dapat dipertimbangkan untuk anak-anak usia 5 tahun ke atas. Dosis harian dapat dibagi menjadi 1 hingga 4 administrasi. Dosis maksimal dalam satu kali pemberian tidak boleh lebih dari 3 mg. Pengobatan dengan Pulmicort Respules untuk eksaserbasi akut dapat dilanjutkan sampai perbaikan klinis, namun tidak lebih dari 10 hari.

Eksaserbasi Penyakit Paru Obstrukstif Kronis (PPOK)

Dosis harian 4 sampai 8 mg Pulmicort Respules dapat diberikan, dan dibagi 2 hingga 4 administrasi, sampai perbaikan klinis namun tidak lebih dari 10 hari.

Instruksi penggunaan Pulmicort Respules

- Persiapkan nebuliser untuk diisi.
- Lepaskan satu Pulmicort Respules dari rangkaian obat dengan memutar obat secara kuat. Tinggalkan sisanya dalam wadah foil.
- Kocok Respules
- Putar bagian atas Respules
- Tekan isi dan tuangkan ke dalam wadah nebuliser. Jangan larutkan isi, kecuali diinstruksikan oleh dokter. Pada beberapa kasus, mungkin hanya perlu digunakan sebagian Respules untuk menyesuaikan dengan dosis yang diresepkan. Ikuti petunjuk medis dari dokter atau apoteker.
- Gunakan nebuliser sesuai petunjuk, pastikan isi dalam wadah terpakai seluruhnya.
- Setelah digunakan, bersihkan nebuliser sesuai petunjuk dari pembuat alat. Ingatlah untuk membersihkan wajah dan mulut Anda dengan air. Setelah setiap nebulisasi, *mouthpiece* atau *facemask* sebaiknya direndam dalam air hangat, lalu dikeringkan.

Semua larutan yang digunakan dalam nebuliser harus memproduksi ukuran dan dan kekuatan uap (aerosol) yang tepat, agar dapat berkhasiat pada paru-paru Anda. Pada Pulmicort Respules, hal ini dapat tercapai dengan menggunakan nebuliser udara bertekanan jet (*compressed air jet*) yang memberikan keluaran minimal 6 hingga 8 liter per menit. Jet nebuliser menghasilkan uap yang dipompa dari kompresor listrik atau kompresor oksigen dari tangki. Perhatikan petunjuk manual dari nebuliser yang digunakan.

Informasi penting tentang gejala asma Anda

Penting untuk mengetahui bahwa nebuliser ultrasonic tidak direkomendasikan untuk penggunaan Pulmicort Respules, karena menghasilkan sinyal frekuensi tinggi yang menggetarkan cairan dan menghasilkan droplet cairan yang beresiko terhirup saat digunakan. Hal ini dapat mengakibatkan Pulmicort Respules tidak bekerja dengan baik.

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Dokter Anda harus memberi tahu Anda cara terbaik untuk mengelola gejala dan serangan sesak nafas Anda. Ini mungkin termasuk obat-obatan tambahan (seperti obat-obatan pereda) untuk digunakan ketika Anda mengalami serangan sesak nafas mendadak.

Jika Anda menggunakan lebih banyak obat Pereda pernafasan atau Anda mengalami sesak napas lebih dari biasanya, beritahu dokter Anda. Jika keadaan Anda memburuk, dokter Anda mungkin memberi Anda beberapa obat tambahan (seperti kortikosteroid oral atau antibiotik).

Jika Anda melewatkan dosis Pulmicort Respules, lompati dosis yang terlewat dan gunakan dosis selanjutnya seperti biasa. Jangan gunakan dosis ganda untuk menebus dosis yang Anda lewatkan. Ini dapat meningkatkan kemungkinan Anda mendapatkan efek samping yang tidak diinginkan.

4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mendapatkannya.

Jika salah satu dari hal berikut terjadi pada Anda, bicaralah kepada dokter Anda:

- Infeksi jamur di mulut. Ini dapat dihindari bila Anda mencuci mulut dengan air setelah menggunakan Pulmicort.
- Nyeri tenggorokan sedang, batuk dan suara serak.
- Pneumonia (infeksi paru-paru) dalam pasien COPD.
- Merasa cemas, gelisah dan tegang.
- Suasana hati berubah.
- Gemetaran.
- Katarak.
- Kram otot.
- Pandangan kabur.
- Ruam pada wajah, yang dapat dihindari dengan mencuci wajah dengan air setelah menggunakan *face mask*.

- Kesulitan tidur, terlalu gembira atau kesal, biasanya terjadi pada anak-anak.
- Memar pada kulit.
- Suara hilang.

Bicaralah pada dokter Anda jika saat menggunakan budesonide terjadi hal-hal berikut:

- Demam atau menggigil.
- Bertambahnya produksi mukus/lendir, perubahan pada warna lendir.
- Bertambahnya batuk atau kesulitan bernafas.

Anda mungkin mengalami gejala infeksi paru-paru.

Jika salah satu dari hal berikut terjadi pada Anda, bicaralah segera kepada dokter Anda:

- Bengkak pada wajah,terutama di area sekitar mulut (mungkin terjadi pembengkakan di area bibir, lidah, mata, telinga), ruam, gatal, dermatitis kontak (masalah kulit), bronkospasme (menegangnya otot di saluran nafas menyebabkan mengi). Ini artinya Anda mengalami reaksi alergi. Reaksi ini jarang terjadi, dimana probabilitas kejadian adalah 1 dalam 1000 orang.
- Sesak mengi tiba-tiba setelah menghirup obat Anda. Hal ini juga jarang terjadi, kurang dari 1 dalam 10.000 orang.

Ini mungkin efek samping yang serius. Efek samping yang serius jarang terjadi.

Kortikosteroid inhalasi dapat berefek pada produksi hormon di tubuh Anda, terutama bila dosis tinggi digunakan dalam jangka waktu yang lama. Efek tersebut adalah:

- Perubahan pada kepadatan mineral tulang.
- Glaukoma (bertambahnya tekanan di mata).
- Pertumbuhan anak dan remaja yang lambat (jarang). Jika dosis tinggi digunakan selama beberapa tahun, tinggi akhir mungkin berkurang hingga 1 cm.
- Berefek pada kelenjar adrenal (kelenjar kecil di sebelah ginjal) (jarang).

Efek-efek ini lebih jarang terjadi pada penggunaan kortikosteroid inhalasi dibanding kortikosteroid tablet.

Pelaporan efek samping

Jika anda mengalami efek samping, diskusikan dengan dokter, apoteker atau perawat anda. Ini dapat termasuk efek samping yang tidak disebutkan dalam leaflet ini. Dengan melaporkan efek samping, anda juga dapat menambah informasi mengenai keamanan obat ini. Untuk melaporkan efek samping, anda dapat menghubungi nomor: +628121064222 atau email: AE.Indonesia@astrazeneca.com

5. Cara menyimpan Pulmicort Respules

- Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
- Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tercantum pada karton atau pada label inhaler. Tanggal kadaluwarsa mengacu pada hari terakhir bulan itu.
- Jangan menyimpan di atas suhu 30ºC. Jangan dibekukan. Simpan dalam posisi tegak lurus. Simpan Pulmicort Respules dalam box dan foil aslinya, hindari dari sinar matahari.
- Setelah foil dibuka, respules di dalamnya harus digunakan dalam jangka waktu 3 bulan. **Catatan:** sebaiknya beri tanda kapan waktu foil dibuka untuk membantu sebagai pengingat.
- Apabila hanya sebagian suspensi digunakan, sisa suspensi dalam Respules harus segera dibuang.
- Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Apa kandungan Pulmicort Respules 0.25 mg/mL dan 0.5 mg/mL

Kandungan zat aktif Pulmicort Respules adalah budesonide. Setiap Pulmicort Respule 0.25 mg/mL dan 0.5 mg/mL mengandung 0.25 dan 0.5 mg zat aktif, yaitu budesonide.

Bahan tambahan lainnya adalah disodium edetate, sodium chloride, polysorbate 80, citric acid, sodium citrate dan water for injections.

Seperti apa Pulmicort Respules 0.25 mg/mL ; 0.5 mg/mL dan isi kemasannya

Setiap Respule mengandung 2 mililiter (mL) larutan steril.

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Larutan harus dinebulisasi (dibuat menjadi kabut halus) sebelum dapat dihirup.

Pulmicort respules 0.25 mg/mL dan 0.5 mg/mL dibuat menjadi 5 buah tiap strip dan dibungkus dalam foil envelope. Tiap karton berisi 20 Respules.

Kemasan:

Dus, terdiri dari 4 pouch berisi 5 respules dengan kekuatan 0.25 mg/mL

Dus, terdiri dari 4 pouch berisi 5 respules dengan kekuatan 0.5 mg/mL

Diproduksi oleh

AstraZeneca AB

Forskargatan 18, SE-151 85

Södertälje, Sweden

Dan

AstraZeneca Pty, Ltd

10 -14 Khartoum Road, North Ryde NSW 2113

Australia

Diimport oleh:

PT. AstraZeneca Indonesia

Cikarang, Bekasi – Indonesia

HARUS DENGAN RESEP DOKTER

Nomor Izin Edar : DKI1151302568A1 (0.25 mg/mL)

DKI1151302568B1 (0.5 mg/mL)

Leaflet ini terakhir direvisi pada 21 Februari 2023