ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kinpeygo 4 mg modified-release hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release hard capsule contains budesonide 4 mg.

Excipient(s) with known effect

Each capsule contains 230 mg of sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release hard capsule.

19 mm white coated opaque capsules printed with “CAL10 4MG” in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kinpeygo is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g).

4.2 Posology and method of administration

Posology

The recommended dose is 16 mg once daily in the morning, at least one hour before a meal, for an initial duration of 9 months. When treatment is to be discontinued, the dose should be reduced to 8 mg once daily for 2 weeks of therapy; the dose may be reduced to 4 mg once daily for an additional 2 weeks, at the discretion of the treating physician.

Re-treatment may be considered at the discretion of the treating physician. Safety and efficacy of treatment with subsequent courses of Kinpeygo have not been established.

If the patient forgets to take Kinpeygo, the patient should take Kinpeygo the next day, in the morning as usual. The patient should not double the daily dose to make up for a missed dose.

Special populations
Elderly
Experience of the use of Kinpeygo in the elderly is limited. However, from the clinical data available, the efficacy and safety of Kinpeygo are expected to be similar to that of other age groups studied.

Hepatic impairment
The safety and efficacy of Kinpeygo capsules in patients with hepatic impairment have not been studied.

Kinpeygo is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C). See section 4.3, 4.4 and 5.2.

Renal impairment
The pharmacokinetics of budesonide are not expected to be altered in patients with renal impairment.

Paediatric population
The safety and efficacy of Kinpeygo capsules in children and adolescents below 18 years of age have not yet been established. No data are available.

Method of administration

Kinpeygo is for oral use. The modified-release hard capsules should be swallowed whole with water in the morning, at least 1 hour before a meal (see section 5.2). The capsules must not be opened, crushed or chewed, as it could affect the release profile.

4.3 Contraindications

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

Patients with severe hepatic impairment (Child-Pugh Class C).

4.4 Special warnings and precautions for use

Hypercorticism and adrenal axis suppression

When glucocorticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Glucocorticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic glucocorticosteroid is recommended.

Since Kinpeygo contains a glucocorticosteroid, general warnings concerning glucocorticosteroids, as given below, should be followed.

Hepatic impairment

Patients with moderate or severe hepatic impairment (Child-Pugh Class B or C respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure of oral budesonide. Patients with moderate hepatic impairment (Child-Pugh Class B) should be monitored for increased signs and/or symptoms of hypercorticism.

Symptoms of steroid withdrawal in patients transferred from systemic corticosteroids

Patients who are transferred from glucocorticosteroid treatment with high systemic availability to glucocorticosteroids with lower systemic availability, such as budesonide, should be monitored since symptoms attributed to withdrawal of steroid therapy, including those of acute adrenal axis suppression or benign intracranial hypertension, may develop. Adrenocortical function monitoring may be required in these patients and the dose of glucocorticosteroid treatment with high systemic effects should be reduced cautiously.

Replacement of systemic glucocorticosteroids with budesonide may unmask allergies (e.g., rhinitis and eczema), which were previously controlled by the systemic medicinal product.

Infections

Patients who are on medicinal products that suppress the immune system are more susceptible to infection than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of glucocorticosteroids. In patients who have not had these diseases, particular care should be taken to avoid exposure.

How the dose, route, and duration of glucocorticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior glucocorticosteroid treatment to the risk is also not known. If exposed to chickenpox, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See Summaries of Product Characteristics for VZIG and IG.) If chickenpox develops, treatment with antiviral agents may be considered.

Glucocorticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections, or ocular herpes simplex.

Caution with special diseases

Patients with infections, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where use of glucocorticosteroids may be associated with an increased risk of adverse effects, should be monitored.

Visual disturbance

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

Concomitant treatment with potent CYP3A4 inhibitors

Concomitant treatment with potent CYP3A4 inhibitors, including ketoconazole and cobicistat-containing products, is expected to increase the risk of systemic side effects attributable to budesonide. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticosteroid side effects. If this is not possible, the period between treatments should be as long as possible and a reduction of the budesonide dose to 8 mg budesonide daily could also be considered (see section 4.5).

After extensive intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure to budesonide after oral administration increased approximately two-fold. As with other medicinal products primarily metabolised through CYP3A4, regular ingestion of grapefruit or its juice should be avoided in connection with Kinpeygo administration (other juices such as orange juice or apple juice do not inhibit CYP3A4). See also section 4.5.

ACTH stimulation test

Because adrenal function may be suppressed, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

Sucrose

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products/substances inhibiting CYP3A4

Budesonide is metabolised via CYP3A4. Potent inhibitors of CYP3A4 can increase plasma levels of budesonide. Co-administration of the potent CYP3A4 inhibitor ketoconazole or intake of grapefruit juice resulted in a 6.5-fold and 2-fold increase, respectively in the bioavailability of budesonide, compared to budesonide alone.

Thus, clinically relevant interactions with potent CYP3A inhibitors, such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, cyclosporine, and grapefruit juice, are to be expected, and may increase systemic budesonide concentrations (see sections 4.4 and 5.2).

Medicinal products/substances inducing CYP3A4

Concomitant treatment with CYP3A4 inducers such as carbamazepine may reduce budesonide systemic exposure.

Medicinal products/substances metabolised by CYP3A4

Given its low affinity for CYP3A4 and P-gp, as well as the formulation, pharmacokinetic (PK) characteristics and low systemic exposure, Kinpeygo is unlikely to affect the systemic exposure of other medicinal products.

Oral contraceptives

Oral contraceptives containing ethinyl estradiol, which are also metabolised by CYP3A4, do not affect the pharmacokinetics of budesonide.

Proton pump inhibitors

The pharmacokinetics of budesonide have not been evaluated in combination with proton pump inhibitors (PPIs). In a study assessing intragastric and intraduodenal pH in healthy volunteers after repeated dosing with the PPI omeprazole 40 mg once daily, intragastric and intraduodenal pH did not exceed that required for disintegration of Kinpeygo. Beyond the duodenum, PPIs such as omeprazole are unlikely to affect pH.

Other interactions to be considered

Budesonide treatment may reduce serum potassium, which should be considered when Kinpeygo is co-administered with a medicinal product where the pharmacological effects may be potentiated by low serum potassium, such as cardiac glucosides, or when co-administered with diuretics that lower serum potassium.

4.6 Fertility, pregnancy and lactation

Pregnancy

Administration during pregnancy should be avoided unless there are compelling reasons for therapy with Kinpeygo. There are only few data of pregnancy outcomes after oral administration of budesonide in humans. Although data on the use of inhaled budesonide in a large number of exposed pregnancies indicate no adverse effect, the maximal concentration of budesonide in plasma is expected to be higher in association with treatment with Kinpeygo compared to inhaled budesonide. In pregnant animals budesonide, like other glucocorticosteroids, has been shown to cause abnormalities of fetal development (see section 5.3). The relevance of this to man has not been established.

Therefore, Kinpeygo should not be used during pregnancy unless the clinical condition of the woman requires treatment with budesonide. The expected benefits for the pregnant woman have to be weighed against the potential risk for the fetus.

Budesonide was found to cross the placental barrier. The relevance of this observation to humans has not been established.

Hypoadrenalism may occur in neonates exposed to glucocorticosteroids in utero; carefully observe neonates for signs and symptoms of hypoadrenalism.

Breast-feeding

Budesonide is excreted in breast milk.

Lactation studies have not been conducted with oral budesonide, including Kinpeygo, and no information is available on the effects of the medicinal product on the breast-fed infant or the effects of the medicinal product on milk production. A risk to the breast-fed infant cannot be excluded.

If Kinpeygo is used when a mother is breast-feeding, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from budesonide therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of budesonide on human fertility. There were no effects on fertility in rats after treatment with budesonide.

4.7 Effects on ability to drive and use machines

No studies on the effects of Kinpeygo on the ability to drive and use machines have been performed. It is expected that Kinpeygo has no or negligible influence on the ability to drive or use machinery.

4.8 Undesirable effects

Summary of the safety profile

In the Kinpeygo phase 3 clinical study the most commonly reported adverse drug reactions were acne reported in approximately 10% of patients, peripheral oedema, face oedema, weight increased and white blood cell count increased, each occurring in approximately 5% of patients; these were mainly of mild or moderate severity and reversible, reflecting the low systemic exposure to budesonide after oral administration.

Tabulated list of adverse reactions

Adverse drug reactions reported in the pivotal phase 3 clinical study and from post-marketing data with Kinpeygo are presented in Table 1.

Adverse reactions reported are listed according to the following frequency: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 1: Adverse drug reactions by frequency and system organ class

MedDRA system organ classification	**Frequency**	**Reaction**
Blood and lymphatic system disorders	Common Common	White blood cell count increased Neutrophil count increased
Endocrine disorders	Common	Cushingoid
Metabolism and nutrition disorders	Very common Common	Hypokalaemia Diabetes mellitus*
Eye disorders	Rare	Vision blurred (see also section 4.4)
Vascular disorders	Common	Hypertension
Gastrointestinal disorders	Common	Dyspepsia
Skin and subcutaneous tissue disorders	Very common	Skin reactions (acne, dermatitis)
Musculoskeletal and connective tissue disorders	Common	Muscle spasms
General disorders and administration site conditions	Common Common Common	Oedema peripheral Face oedema Weight increased

* All patients with new onset of diabetes diagnosed during or following Kinpeygo treatment had levels of FBG and HbA1c prior to the start of treatment that were indicative of pre-diabetes (HbA1c ≥ 5.7% or FBG≥100 mg/dL).

Description of selected adverse reactions

Potential class effects
Adverse drug reactions typical of systemic glucocorticosteroids may occur (e.g., cushingoid features, increased blood pressure, increased risk of infection, delayed wound healing, reduced glucose tolerance, sodium retention with oedema formation, muscle weakness, osteoporosis, glaucoma, mental disorders, peptic ulcer, increased risk of thrombosis). These adverse drug reactions are dependent on dose, treatment time, concomitant and previous glucocorticosteroid intake, and individual sensitivity. Not all of these adverse reactions were observed in the clinical study program of Kinpeygo.

Paediatric population

No data available.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Reports of acute toxicity or death following overdose of glucocorticosteroids are rare. Acute overdose, even in excessive doses, is not expected to lead to clinically significant consequences. In the event of acute overdose, no specific antidote is available. Treatment consists supportive and symptomatic therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidiarrheals, intestinal antiinflammatory/antiinfective agents, corticosteroids acting locally, ATC code: A07EA06

Mechanism of action

The intended action of Kinpeygo is the suppression of mucosal B-cells, located in the Peyer's patches in the ileum where the majority of galactose-deficient IgA1 antibodies (Gd-IgA1) are produced. The inhibition of their proliferation and differentiation into plasma cells is expected to lower the occurrence of Gd-IgA1 antibodies and hence the formation of immune complexes in the systemic circulation, therefore preventing the downstream effects of glomerular mesangial deposition of immune complexes containing Gd-IgA1, manifesting as glomerulonephritis and loss of renal function.

Pharmacodynamic effects

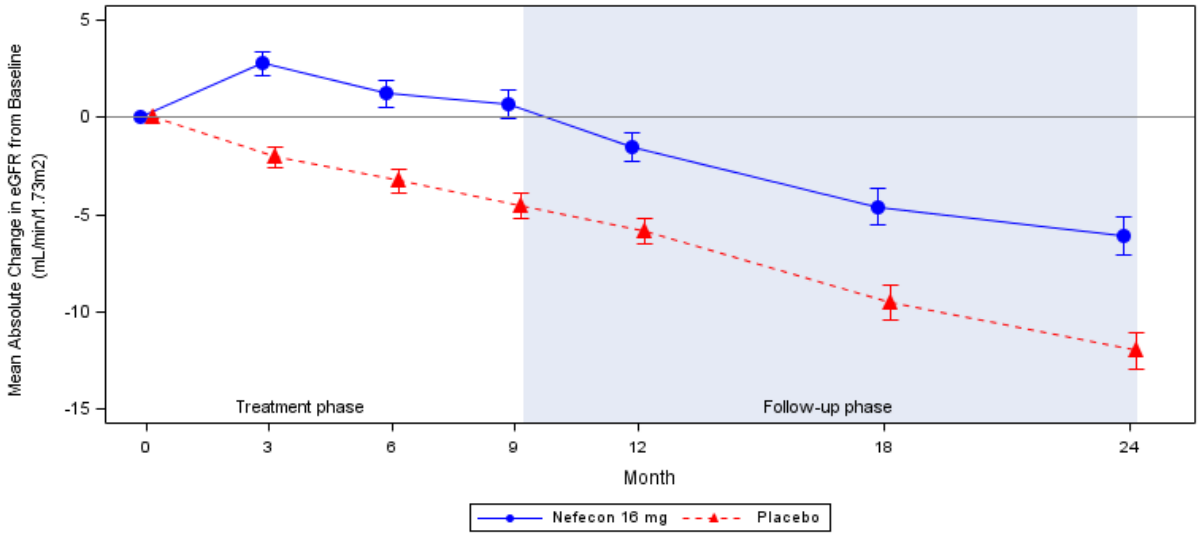
Kinpeygo is an oral, modified-release hard capsule formulation of budesonide which combines a delayed capsule disintegration with a prolonged release of the active substance budesonide in the ileum. By directing the release of budesonide to the ileum, where Peyer's patches reside in high density, a local pharmacological effect is anticipated.

Clinical efficacy

Primary IgA nephropathy
The efficacy of Kinpeygo has been evaluated in 2 randomised, double-blind, placebo-controlled studies of patients with primary IgAN, who were receiving optimised dose (maximum allowed dose or maximum tolerated dose) of Renin-Angiotensin System (RAS) inhibitor therapy as a standard of care (SOC). The effect of Kinpeygo on kidney function decline based on estimated glomerular filtration rate (eGFR) and proteinuria reduction based on urine protein creatinine ratio (UPCR) was assessed in a randomised, double-blind, multicentre phase 3 study in patients with biopsy proven IgAN. 364 patients in the Full Analysis Set were randomised 1:1 to either Kinpeygo 16 mg once daily or placebo and treated for 9 months followed by a 2-week taper phase of 8 mg and 15 months of observational follow-up.

The final analysis of the study demonstrated that over the 2-year period, a 9-month treatment course of Kinpeygo (Nefecon) 16 mg/day reduced the loss of kidney function at 2 years in patients with primary IgAN in a statistically significant manner. The eGFR benefit accrued by the end of 9 months of treatment was maintained during 15 months of observational follow-up (Figure 1).

Figure 1: Mean absolute change in eGFR from baseline in Phase 3 NefIgArd Study



The treatment effect eGFR difference at 2 years was 6.00 mL/min/1.73 m2 using the MMRM analysis without explicit missing data assumptions (MAR assumption) and was statistically significant. The change from baseline in eGFR at 24 months was -7.50 mL/min/1.73 m2 in the Kinpeygo group compared to -13.50 mL/min/1.73 m2 in the placebo group; there was a treatment benefit of 6.00 mL/min/1.73 m2 (95% CI: 2.76 to 10.08) with Kinpeygo treatment compared to placebo (Table 2).

A supplementary analysis of 2-year eGFR total slope using a linear spline mixed effects analysis method to account for the acute (baseline to 3 months) and chronic (from 3 months onwards) phases estimated an overall treatment benefit of 2.62 mL/min/1.73 m^2 per year (95% CI 1.23 to 4.00) in favour of Kinpeygo (Table 2).

Table 2: Analysis of eGFR at 24 months in Phase 3 NefIgArd Study

eGFR (CKD-EPI) (mL/min/1.73 m^2) [a]	**Kinpeygo 16 mg (N=182)**	**Placebo (N=182)**
Mean change from baseline (mL/min/1.73 m^2) at 24 months (15 months after Kinpeygo treatment ended) [b]	-7.50	-13.50
Kinpeygo 16 mg versus Placebo: (95% CI) Change from baseline in eGFR at 24 months (mL/min/1.73 m^2) [b] 2-year eGFR total slope (mL/min/1.73 m^2 per year) [c]	6.00 (2.76 to 10.08) 2.62 (1.23 to 4.00)	

a Including all observed eGFR data recorded after use of prohibited medication.
b Adjusted geometric least squares mean ratio of eGFR relative to baseline analysed using mixed model repeated measures analysis. Mean changes derived directly from the analysis performed on a log scale.
c Linear-spline mixed effects model in which eGFR was modelled simultaneously and separately over the acute (baseline to 3 months) and chronic (from 3 months onwards) phases and then combined to estimate the overall total slope. Data not log-transformed and including all observed eGFR data regardless of the use of prohibited medications or starting dialysis or having a renal transplant.
CI: confidence interval; eGFR (CKD-EPI): estimated glomerular filtration rate based on Chronic Kidney Disease Epidemiology Collaboration calculation

The 2-year eGFR treatment effect was consistent across all key subgroups, including key demographic (such as age, sex, race) and baseline disease (such as baseline proteinuria) characteristics.

The time to a confirmed 30% reduction in eGFR or end-stage renal disease (defined as renal-related death, renal transplantation, dialysis, or sustained eGFR <15 mL/min/1.73 m^2) was delayed in patients who received Kinpeygo compared with those who received placebo (HR 0.45; 95% CI 0.26 to 0.75). The proportion of patients with a confirmed event over the 2-year study period was 11.5% in the Kinpeygo group versus 21.4% of patients in the placebo group.

The final analysis of treatment effect on proteinuria at 2 years was consistent with that observed at the end of the 9 months course of Kinpeygo treatment. However, in the Kinpeygo treatment arm proteinuria increased after a peak reduction at 12 months (Table 3). The UPCR treatment effect at 9 months was highly consistent across subgroups, including key demographic (such as age, sex, race) and baseline disease (such as baseline proteinuria) characteristics. A similarly consistent pattern in UPCR across subgroups was observed at 2 years.

Table 3: Proteinuria reduction at 9, 12, and 24 months and averaged over 12 to 24 months in Phase 3 NefIgArd Study

Percentage reduction from baseline in UPCR g/g [a, b]	**Kinpeygo 16 mg (N=182)**	**Placebo (N=182)**
At 9 months [c]	34%	5%
At 12 months (3 months after Kinpeygo treatment ended)	51%	3%
At 24 months (15 months after Kinpeygo treatment ended)	31%	1%
Kinpeygo 16 mg versus placebo: Average UPCR percentage reduction over 12 to 24 months compared to baseline [d] (95% CI)	41% (32% to 49%)	

a Excluding UPCR data recorded after use of prohibited medication.
b Adjusted geometric least squares mean ratio of UPCR relative to baseline were based on a longitudinal repeated measures model.
c Percent reduction in UPCR was previously evaluated in the first 199 patients randomised (p=0.0003). The final analysis in all 364 patients confirmed a 30% reduction in UPCR at 9 months with Kinpeygo compared with placebo (95% CI 20% to 39%).
d Average UPCR percentage reduction during follow-up (over 12 to 24 months) based on longitudinal repeated measures model.
CI: confidence interval; UPCR: urine protein creatinine ratio.

A supportive phase 2b study with a similar study design was conducted in a total of 153 randomised patients who received Kinpeygo 16 mg, Kinpeygo 8 mg, or placebo, once daily for 9 months followed by a 2-week taper phase and 3 months of observational follow-up, while continuing to receive RAS inhibitor therapy.

The primary objective was met at an interim analysis that compared Kinpeygo to placebo and showed a statistically significant reduction in UPCR at 9 months for the combined Kinpeygo 16 mg/day and 8 mg/day dose groups compared to placebo (p=0.0066).

Using the same statistical methodology as in the phase 3 study, a statistically significant 26% reduction in the primary endpoint UPCR was shown at 9 months for the 16 mg dose of Kinpeygo versus placebo (p=0.0100) and a 29% reduction at 12 months (p=0.0027).

The difference in eGFR CKD-EPI (serum creatinine) for the 16 mg dose of Kinpeygo versus placebo was 3.57 mL/min/1.73m^2 at 9 months (p=0.0271), and 4.46 mL/min/1.73 m^2 at 12 months (p=0.0256). The improvement in 1-year eGFR slope was estimated to be 5.69 mL/min/1.73 m^2 per year with Kinpeygo 16 mg once daily compared to placebo (p=0.0007).

Paediatric population

Kinpeygo has not been studied in the paediatric population.

5.2 Pharmacokinetic properties

Absorption

The Kinpeygo formulation is designed to deliver budesonide topically in the ileum. Oral absorption of budesonide seems to be complete and is rapid, whereas systemic bioavailability due to high first-pass metabolism is low (approximately 10%).

Following single oral administration of Kinpeygo 16 mg to healthy subjects, the geometric mean C_{max} ranged between 3.2 and 4.4 ng/mL, and $AUC_{(0-24)}$ ranged between 24.1 and 24.8 ng/mL×h.

There was no clinically relevant food effect observed on the overall systemic exposure of budesonide when either a moderate or high fat meal was consumed 1 hour after dosing.

Distribution

Budesonide is rapidly and extensively distributed into tissues and organs. Approximately 85 to 90% of budesonide binds to plasma proteins in blood over the concentration range of 1 to 100 nmol/L. The volume of distribution at steady state is 3 to 4 L/kg.

Biotransformation

Budesonide is rapidly metabolised by the liver (and to lesser extent the gut), primarily by oxidative pathways via CYP3A4 to two main metabolites, 16α-hydroxyprednisolone and 6β-hydroxybudesonide, which have less than 1% of the glucocorticosteroid receptor affinity and anti-inflammatory activity of budesonide.

The metabolism of budesonide is 2- to 5-fold faster than that of hydrocortisone and 8- to 15-fold faster than that of prednisolone.

Elimination

Budesonide has a high clearance rate of approximately 72 to 80 L/h, which is close to the estimated liver blood flow, and, accordingly, suggests that budesonide is a high hepatic clearance medicinal product.

$T_{½}$ for budesonide after dosing with Kinpeygo ranged from 5 to 6.8 hours in healthy volunteer studies.

Budesonide is excreted in urine and feces in the form of metabolites. The major metabolites, including 16α-hydroxyprednisolone and 6β-hydroxybudesonide, are mainly renally excreted, intact or in conjugated forms. No unchanged budesonide was detected in urine.

Hepatic impairment

Budesonide is predominantly metabolised by hepatic biotransformation.
In subjects with moderate hepatic impairment (Child-Pugh class B), systemic availability of orally administered budesonide was 3.5-fold higher (27%) compared with healthy volunteers (systemic availability 7.4%); there was no clinically relevant increase in systemic availability in patients with mild hepatic impairment (Child-Pugh class A).

Patients with severe hepatic impairment have not been studied.

Renal impairment

Intact budesonide is not excreted renally. The main metabolites of budesonide, which have negligible glucocorticosteroid activity, are largely (60%) excreted in urine.

Paediatric population

Kinpeygo was not studied in the paediatric population.

5.3 Preclinical safety data

The preclinical safety of budesonide has been documented in studies during the development of other formulations of this compound. No preclinical studies have been conducted with the Kinpeygo formulation itself.

Results from acute, subacute and chronic toxicity studies show that the systemic effects of budesonide, e.g. decreased body-weight gain and atrophy of lymphoid tissues and adrenal cortex, are less severe or similar to those observed after administration of other glucocorticosteroids.

Budesonide, evaluated in six different test systems, did not show any signs of mutagenic or clastogenic effects.

An increased incidence of brain gliomas in male rats in a carcinogenicity study could not be verified in a repeat study, in which the incidence of gliomas did not differ between any of the groups on active treatment (budesonide, prednisolone, triamcinolone acetonide) and the control group.

Liver changes (primary hepatocellular neoplasms) found in male rats in the original carcinogenicity study were noted again in the repeat study with budesonide, as well as the reference glucocorticosteroids. These effects are most probably related to a receptor effect and thus represent a class effect in this species.

Available clinical experience shows that there are no indications that budesonide or other glucocorticosteroids induce brain gliomas or primary hepatocellular neoplasms in humans.

Budesonide had no effect on fertility in rats. In pregnant animals, budesonide, like other glucocorticoids, has been shown to caues foetal death and abnormalities of foetal development (smaller litter size, intrauterine growth retardation of foetuses and skeletal abnormalities). The clinical relevance of these findings to human has not been established (see section 4.6).

The toxicity of budesonide modified-release hard capsules, with focus on the gastro-intestinal tract, has been studied in cynomolgus monkeys at doses of up to 5 mg/kg (approximately 15 times the recommended daily dose of Kinpeygo in humans on a dose per body weight basis) after repeated oral administration for up to 6 months. No effects were observed in the gastrointestinal tract, either from gross pathology or histopathological examination.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Sugar spheres (sucrose and corn starch)

Hypromellose
Macrogol
Citric acid monohydrate
Ethylcellulose
Medium chain triglycerides
Oleic acid

Capsule shell

Hypromellose
Macrogol
Titanium dioxide (E171)
Methacrylic acid - methyl methacrylate co-polymers
Talc
Dibutylsebacate

Printing ink

Shellac
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 25°C .

6.5 Nature and contents of container

White high density polyethylene (HDPE) bottle with a white polypropylene (PP) child-resistant closure with an induction seal.
Pack sizes: 1 bottle containing 28 or 120 modified-release hard capsules and multipacks containing 360 (3 packs of 120) modified-release hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse 2-18
61118 Bad Vilbel

Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1657/001
EU/1/22/1657/002
EU/1/22/1657/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 July 2022
Date of latest renewal: 17 June 2024

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Tjoapack Netherlands B.V.
Nieuwe Donk 9
4879 AC Etten-Leur
Noord-Brabant
Netherlands

STADA Arzneimittel AG
Stadastrasse 2 – 18
61118 Bad Vilbel
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton

1. NAME OF THE MEDICINAL PRODUCT

Kinpeygo 4 mg modified-release hard capsules
budesonide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 4 mg budesonide.

3. LIST OF EXCIPIENTS

Sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release capsule, hard

28 modified-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow whole with water in the morning, one hour before a meal. Do not open, crush or chew.

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C .

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse 2-18
61118 Bad Vilbel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1657/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

16. INFORMATION IN BRAILLE

Kinpeygo 4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton

1. NAME OF THE MEDICINAL PRODUCT

Kinpeygo 4 mg modified-release hard capsules
budesonide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 4 mg budesonide.

3. LIST OF EXCIPIENTS

Sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release capsule, hard

120 modified-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow whole with water in the morning, one hour before a meal. Do not open, crush or chew.

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C .

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse 2-18
61118 Bad Vilbel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1657/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

16. INFORMATION IN BRAILLE

Kinpeygo 4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle label.

1. NAME OF THE MEDICINAL PRODUCT

Kinpeygo 4 mg modified-release hard capsules
budesonide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 4 mg budesonide.

3. LIST OF EXCIPIENTS

Sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release capsule, hard

28 modified-release hard capsules.
120 modified-release hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow whole with water in the morning, one hour before a meal. Do not open, crush or chew.

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C .

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse 2-18
61118 Bad Vilbel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1657/001 120 modified-release hard capsules
EU/1/22/1657/002 360 modified-release hard capsules (3 packs of 120)
EU/1/22/1657/003 28 modified-release hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF BOTTLE MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kinpeygo 4 mg modified-release hard capsules
budesonide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 4 mg budesonide.

3. LIST OF EXCIPIENTS

Sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release capsule, hard

Multipack: 360 (3 packs of 120) modified-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow whole with water in the morning, one hour before a meal. Do not open, crush or chew.

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C .

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse 2-18
61118 Bad Vilbel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1657/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

16. INFORMATION IN BRAILLE

Kinpeygo 4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF BOTTLE MULTIPACK (WITHOUT BLUE BOX AND WITHOUT UNIQUE IDENTIFIER)

1. NAME OF THE MEDICINAL PRODUCT

Kinpeygo 4 mg modified-release hard capsules
budesonide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 4 mg budesonide

3. LIST OF EXCIPIENTS

Sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release capsule, hard

120 modified-release hard capsules.
Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow whole with water in the morning, one hour before a meal. Do not open, crush or chew.

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C .

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse 2-18
61118 Bad Vilbel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1657/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kinpeygo 4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kinpeygo 4 mg modified-release hard capsules
budesonide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kinpeygo is and what it is used for

Kinpeygo contains the active substance budesonide, a corticosteroid medicine which mainly acts locally in the intestine to reduce the inflammation associated with primary immunoglobulin A (IgA) nephropathy.

Kinpeygo is used to treat primary IgA nephropathy in adults 18 years of age or older.

2. What you need to know before you take Kinpeygo

Do not take Kinpeygo:
- If you are allergic to budesonide or any of the other ingredients of this medicine (listed in section 6).
- If you have loss of function of your liver that your doctor has told you is “severe”.

Warnings and precautions
Talk to your doctor or pharmacist before taking Kinpeygo:
- If you are going to have surgery.
- If you have liver problems.
- If you are taking or have recently taken corticosteroids.
- If you have recently had an infection.
- If you have active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections, or ocular herpes simplex.
- If you have high blood pressure.
- If you have diabetes – or someone in your family has had diabetes.
- If you have brittle bones (osteoporosis).
- If you have stomach ulcers.
- If you have glaucoma (increased pressure in the eye) or cataracts – or someone in your family has had glaucoma (increased pressure in the eye).

If any of the above apply to you, you may be at increased risk of side effects. Your doctor will decide on the appropriate measures and if it is still all right for you to take this medicine.

Look out for side effects
If you get blurred vision or other sight problems, contact your doctor. See section 4 for more information.

Chickenpox or measles
Illnesses like chickenpox and measles can be more serious if you are taking this medicine. If you have not yet had these illnesses, keep away from people with chicken pox or measles while taking this medicine. Tell your doctor if you think that you have been infected with chicken pox or measles while taking this medicine.

Adrenal function tests
Kinpeygo could affect the results of adrenal function tests (ACTH stimulation test) ordered by your doctor. Tell your doctors that you are taking Kinpeygo before you have any tests.

Children and adolescents
Kinpeygo should not be used in children and adolescents below 18 years of age. The use of this medicine in children younger than 18 years of age has not been studied.

Other medicines and Kinpeygo
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, and herbal medicines.

This is because Kinpeygo capsules can affect the way some medicines work and some medicines can have an effect on Kinpeygo capsules.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:
- Ketoconazole or itraconazole - to treat infections caused by a fungus.
- Medicines for HIV called 'protease inhibitors' - such as ritonavir, indinavir and saquinavir.
- Erythromycin - an antibiotic used to treat infections.
- Cyclosporin - used to suppress your immune system.
- Carbamazepine - for epilepsy and nerve pain problems.
- Cardiac glycosides - such as digoxin- medicines used to treat heart conditions.
- Diuretics - to remove excess fluid from the body.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Kinpeygo.

Kinpeygo with food and drink
Do not eat grapefruit or drink grapefruit juice while you are taking Kinpeygo. It can affect the way the medicine works.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Do not take this medicine during pregnancy without checking with your doctor first.

Do not take this medicine if you are breast-feeding unless you have checked with your doctor. Budesonide passes in small amounts into the breast milk. Your doctor will help you decide whether you should continue treatment and not breast-feed or if you should stop treatment over the period your baby is being breast-fed.

Driving and using machines

Kinpeygo is not expected to affect your ability to drive or use any machines.

Kinpeygo contains sucrose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Kinpeygo

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How to take
The recommended dose of Kinpeygo is 16 mg (**4 capsules** of Kinpeygo 4 mg) once daily.
Take in the morning, at least 1 hour before a meal.
- Swallow whole with a glass of water.
- Do not open, crush or chew – as this could affect the release of the medicine. The capsules have a special coating, to ensure that the medicine is released in the correct part of your gut.

When treatment is to be discontinued, your doctor will reduce the dose to 8 mg (2 capsules of Kinpeygo 4 mg) once daily for the last 2 weeks of therapy. If considered necessary by your doctor, the dose may then be reduced to 4 mg once daily (1 capsule of Kinpeygo 4 mg) for another 2 weeks.

If you take more Kinpeygo than you should
If you take more Kinpeygo than you should, talk to a doctor or pharmacist straight away. Take the carton with you.

If you have taken more than you should for a long time, the possible side effects listed in section 4 may appear.

If you forget to take Kinpeygo
If you miss a dose of Kinpeygo, wait and take the medicine the next day as usual.
Do not take a double dose to make up for a forgotten dose.

If you stop taking Kinpeygo
Do not stop taking Kinpeygo without discussing it with your doctor first. If you suddenly stop taking the medicine, you may become ill.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor if you notice any of the following side effects with this medicine:

Very common (may affect more than 1 in 10 people)

- Rash or itchy skin
- Acne
- Reduced potassium levels in the blood (hypokalaemia)

Common (may affect up to 1 in 10 people)

- Increased blood pressure
- Swelling of arms or legs – such as ankle swelling

- Swelling of the face
- Cushingoid features such as a rounded face, increased body hair and weight gain
- Indigestion
- Muscle cramps
- Weight gain
- Diabetes mellitus
- Increase in the number of white blood cells (detected by blood tests)

Rare (may affect up to 1 in 1 000 people)

- Blurred vision

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V.* By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Kinpeygo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the bottle label. The expiry date refers to the last day of that month.

Do not store above 25°C .

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Kinpeygo contains
- The active substance is budesonide. Each modified-release hard capsule contains 4 mg of budesonide.

- The other ingredients are:

Capsule content: Sugar spheres (sucrose and corn starch), hypromellose, macrogol, citric acid monohydrate, ethylcellulose, medium chain triglycerides, oleic acid (see also section 2 'Kinpeygo contains sucrose').
Capsule shell: Hypromellose, macrogol, titanium dioxide (E171), methacrylic acid-methyl methacrylate co-polymers, talc, dibutyl sebacate,
Printing ink: Shellac, black iron oxide (E172).

What Kinpeygo looks like and contents of the pack
Kinpeygo 4 mg modified-release hard capsules are 19 mm white coated opaque capsules printed with "CAL10 4MG" in black ink.

The capsules are supplied in a white high-density polyethylene (HDPE) bottle with a white polypropylene (PP) child-resistant closure with an induction seal.
This medicine is available in bottles containing 28 or 120 modified-release hard capsules and in multipacks of 360 modified-release hard capsules comprising 3 bottles, each containing 120 modified-release hard capsules.

Not all pack sizes may be marketed.

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