EU Risk Management Plan for Kinpeygo (budesonide)

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Summary of significant changes in this RMP:	Removal of the black triangle for additional monitoring in Part I; update of post-authorisation exposure data in Part II Module SV.
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QPPV name: Dr. Andreas Iwanowitsch

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Table of contents

List of abbreviations

ACEI	Angiotensin Converting Enzyme Inhibitor
ARB	Angiotensin II type I Receptor Blockers
ATC	Anatomical Therapeutic Chemical
CKD	Chronic Kidney Disease
CSCR	Central Serous Chorioretinopathy
CYP3A4	Cytochrome P450 3A4
DCO	Data Cut Off
FPFV	First Patient First Visit
eCTD	Electronic Common Technical Document
EEA	European Economic Area
eGFR	Estimated Glomerular Filtration Rate
EPAR	European public assessment report
ESRD	End Stage Renal Disease
EU	European Union
FAS	Full Analysis Set
Gd-IgA1	Galactose deficient mucosal Immunoglobulin A1
ICSR	Individual Case Safety Report
IgA	Immunoglobulin A
IgAN	Immunoglobulin A Nephropathy
IgG	Immunoglobulin G
INN	International Nonproprietary Name
LPI	Last Patient In
LPLV	Last Patient Last Visit
MMF	Mycophenolate Mofetil
PSUR	Periodic Safety Update Reports
RAS	Renin-Angiotensin System
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
UPCR	Urine Protein-to-Creatinine Ratio

Part I: Product(s) Overview

Table Part I.1: Product(s) Overview

Active substance(s) (INN or common name)	budesonide
Pharmacotherapeutic group(s) (ATC Code)	A07EA06
Marketing Authorisation Applicant	STADA Arzneimittel AG
Medicinal products to which this RMP refers	Kinpeygo* 4 mg modified-release hard capsules *Kinpeygo is referred to as Nefecon in clinical trials
Invented name(s) in the European Economic Area (EEA)	Kinpeygo
Marketing authorisation procedure	Centralised (Hybrid Application)
Brief description of the product	
Chemical class	Glucocorticosteroid
Summary of mode of action	Kinpeygo is an oral, modified-release hard capsule formulation of the glucocorticosteroid budesonide which combines a delayed capsule disintegration with a prolonged release of the active substance budesonide in the ileum. Kinpeygo is designed to deliver the active ingredient budesonide in the ileum where Peyer's patches are located at high density. The intended action of Kinpeygo is the suppression of mucosal B-cells, located in follicles or Peyer's patches in the ileum, and inhibition of their proliferation and differentiation into plasma cells that produce mucosal galactose-deficientIgA1 antibodies (Gd-IgA1). Consequently, it is expected that the occurrence of Gd-IgA1 antibodies and formation of immune complexes in the systemic circulation will be suppressed, therefore preventing the downstream effects of glomerular mesangial deposition of immune complexes containing Gd-IgA1, manifesting as glomerulonephritis and loss of renal function.

Active substance(s) (INN or common name)	budesonide
Important information about its composition	Well-known active ingredient budesonide incorporated in an innovative modified-release hard capsule formulation targeted to deliver the active substance budesonide in the region of the ileum where the Peyer's patches are located. Each capsule contains 4 mg of the active substance budesonide and 230 mg of the excipient sucrose.
Hyperlink to the Product Information	eCTD Module 1.3.1
Indications in the EEA	
Current	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).
Proposed (if applicable)	Not applicable
Dosage in the EEA	
Current	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.
Proposed (if applicable)	Not applicable
Pharmaceutical form(s) and strengths	
Current	Modified-release hard capsules Each capsule contains 4 mg budesonide
Proposed (if applicable)	Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Treatment of patients with primary immunoglobulin A (IgA) nephropathy (IgAN)

Incidence and prevalence:

IgAN, also known as Berger's disease, is the most common cause of glomerulonephritis worldwide, with prevalence estimates varying from 5% to more than 40% of patients with glomerular disease (Schena and Nistor 2018). It is characterized by the deposition of IgA-containing immune complexes in the glomerular mesangium, leading to inflammation. Children and adolescents with IgAN typically present with painless macroscopic haematuria during an acute upper respiratory tract or gastrointestinal illness, whereas adults usually present with proteinuria, microscopic haematuria, or hypertension. It is a serious, progressive disease that leads to decreasing kidney function and progression to end stage renal disease (ESRD), a state that leads to reduced quality of life and shortened life expectancy, and requires haemodialysis or kidney transplantation for survival.

Demographics of the population in proposed indication and risk factors for the disease:

Primary IgAN can occur at any age, but the clinical onset is common during the second and third decades of life (Donadio and Grande 2002). IgAN progresses to ESRD in up to 50% of patients within 20 years (Lai et al 2016, Moriyama et al 2014). It is the main cause of ESRD in patients with primary glomerular disease who require renal-replacement therapy (Donadio and Grande 2002). It is estimated that IgAN accounts for 10% of renal transplants among patients with primary glomerulonephritis in the US and between 7 to 20% of patients in Europe and Australia in long-term dialysis and renal transplantation programs (Donadio and Grande 2002; Alamartine et al 1991).

Risk factors for disease progression include persistent proteinuria, elevated serum creatinine, microhaematuria, and specific histological lesions (Gallo 1988; Manno et al 2007; Neelakantappa et al 1988). Other risk factors for progressive renal failure include hypertension, reduced GFR, and, to a lesser extent, hyperlipidaemia (Galla 1995; Aucella et al 2009; Floege and Eitner 2011).

The main existing treatment options:

Prior to the approval of Kinpeygo, there were no treatments approved for the management of patients with primary IgAN. Standard of care comprises supportive therapy, which focuses on lowering of proteinuria and optimal blood pressure control by maximum tolerated blockade of the renin-angiotensin system (RAS), together with a low sodium diet (KDIGO 2021).

When proteinuria persists despite optimal RAS inhibition with Angiotensin Converting Enzyme Inhibitor (ACEI)/ Angiotensin II type I Receptor Blockers (ARBs), patients are at risk of progression to ESRD. The KDIGO 2021 guideline recommends such patients should be considered for enrolment in a clinical trial. Although the clinical benefit of systemic glucocorticosteroid (GCS) therapy has not been established, KDIGO 2021 also suggests patients who remain at a high risk of progressive disease can be considered for

a 6-month course of systemic GCS therapy. However, it is noted that the evidence for efficacy is uncertain, and it is emphasised that when systemic corticosteroids are being considered, the important risk of treatment-emergent toxicity must be discussed with patients.

Additional immunosuppressants beyond glucocorticosteroids, such as cyclophosphamide, are suggested for specific situations only, for example in cases of crescentic IgAN where renal function is rapidly deteriorating. Notably, the KDIGO 2021 guideline suggests mycophenolate mofetil (MMF) should not be used in IgAN patients due to heterogeneity of outcomes and potential side effects.

Since the KDIGO 2021 guideline was published, the European Medicines Agency (EMA) has granted CMA for Kinpeygo (budesonide) (7/2022), and the US Food and Drug Administration (FDA) has granted accelerated approval to TARPEYO (budesonide) (12/2021) and FILSPARI (sparsentan) (2/2023) for the treatment of patients with primary IgAN; the EC has granted an orphan designation for sparsentan for the treatment of primary IgAN. SGLT2 inhibitors such as dapagliflozin, whilst not specifically indicated for primary IgAN, may also be used in some patients as an additional supportive care measure.

Natural history of the indicated condition in the population, including mortality and morbidity:

Primary IgAN can occur at any age, but the clinical onset is common during the second or third decades of life (Donadio and Grande 2002). Children and adolescents with IgAN typically present with painless macroscopic haematuria during an acute upper respiratory tract or gastrointestinal illness, whereas adults usually present with proteinuria, microscopic haematuria, or hypertension. The first indication of IgAN, that may be detected incidentally through dipstick or laboratory testing of a urine sample, is usually the appearance of protein and/or blood in the urine (proteinuria and haematuria, respectively), indicating leakage through the damaged glomeruli in the kidney. The diagnosis of IgAN is confirmed by kidney biopsy.

It is a serious, progressive disease that leads to decreasing kidney function and progression to ESRD in up to 50% of patients within 20 years (Lai et al 2016, Moriyama et al 2014, Schena 1990, Vecchio et al 2015, Wyatt and Julian 2013), a disease state that leads to reduced quality of life and shortened life expectancy (Glassock et al 2019, Jarrick et al 2019, Knoop et al 2013), and requires haemodialysis or kidney transplantation for survival.

Important co-morbidities:

IgAN is a proliferative glomerulonephritis, the hallmark of which is the predominance of galactose deficient IgA1 deposits, either alone or with Immunoglobulin G (IgG), IgA, or both, in the glomerular mesangium. The disease can be classified into primary or secondary forms. In the primary form, there are no relevant associated co-morbidities, whereas in the secondary form, the condition may be diagnosed in patients with non-renal diseases, ranging from chronic liver disease and inflammatory states to chronic infections and neoplasms.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable

Part II: Module SIII - Clinical trial exposure

Six healthy volunteer studies have been conducted to support the biopharmaceutics and clinical pharmacology data of Kinpeygo (referred to as Nefecon in clinical studies). In addition, 3 clinical studies have evaluated the efficacy and safety of Nefecon in patients with IgAN.

A summary of the (Nefecon) clinical studies in the proposed indication of primary IgAN is provided in Table 1.

Table 1: Summary of clinical efficacy and safety studies for Nefecon in the treatment of adult patients with primary IgAN

Study identifier	Study Design and type of Control Dates: FPFV to LPLV	Number of Study Sites Location(s)	Diagnosis of patients[b] and key inclusion criteria	Number of patients dosed[a]	Duration of treatment	Gender (% male) Median Age (Range) Race
Nef-301	Randomized, double-blind, placebo-controlled 05 Sep 2018 to 06 Feb 2023	131 sites 20 countries across Europe, North America, South America, and Asia-Pacific including China	Patients on optimized RAS inhibitor therapy with: Proteinuria based on 2 consecutive measurements separated by at least 2 weeks and calculated by the central laboratory showing either ≥1 g per day (≥1000 mg per day) in 2 consecutive measurements or UPCR≥0.8 g/gram (≥90 mg/mmol) in 2 consecutive measurements, and eGFR ≥35 mL/min per 1.73 m^2 and ≤90 mL/min per 1.73 m^2 using the CKD-EPI formula	Nefecon 16 mg: 195 Placebo: 194	9 months	65.3% male Median 42 (20 to 73) years 69.7% White 28.8% Asian
Nef-202	Randomized, double-blind, placebo-controlled 11 Dec 2012 to 25 Jun 2015	61 sites 10 European countries	Patients on optimized RAS inhibitor therapy with: UPCR≥0.5 g/gram (≥56.5 mg/mmol) or urine protein ≥0.75 g/24 hours; and estimated GFR (using CKD-EPI formula) or measured GFR≥45 mL/min per 1.73 m^2	Nefecon 16 mg: 49 Nefecon 8 mg: 51 Placebo: 50	9 months	70.5% male Median 38 (18 to 82) years 96.6% Caucasian
Nef-201	Open-label uncontrolled 09 Jan 2006 to 24 Oct 2008	3 sites Sweden	Patients on current RAS inhibitor therapy with: Proteinuria based on 24-hour urine albumin of >0.5 g and serum creatinine of <200 µmol/L	Nefecon 8 mg: 16	6 months	62.5% male Median 40 (29 to 46) years Race data not available

[a] Patients with a diagnosis of primary IgAN and were treated on a background of RAS inhibitory therapy.

The overall numbers of IgAN patients randomised to Nef-301 and Nef-202, and the numbers included in each of the analysis populations by study and for the pooled safety analyses are summarised in Table SIII.1. For both studies, the Safety Analysis Set includes all patients who received at least 1 dose of study treatment. Data from study Nef-201 and the Nefecon 8 mg dose group in Nef-202 are not included as the focus is the comparison between the approved Nefecon 16 mg dose group and placebo. Therefore, the table is based on a total of 357 patient years exposure to Nefecon 16 mg once daily or placebo from studies Nef-301 and Nef-202.

Table SIII.1: Total patient years exposure to Nefecon 16 mg

	Number of patients					
	Nef-301		**Nef-202**		**Pooled**	
	Nefecon 16 mg	**Placebo**	**Nefecon 16 mg**	**Placebo**	**Nefecon 16 mg**	**Placebo**
Patients randomised[a]	197	198	51	51	248	249
Safety Analysis Set	195	194	49	50	244	244
Total patient years exposure[b]	144.5	147.7	29.3	35.9	173.8	183.6

[a]: In Nef-301, there were 6 patients randomised and not dosed. In Nef-202 there were 3 patients randomised and not dosed. These patients are not included in the safety evaluation.
[b]: Total patient years exposure estimated from mean exposure×number of patients.

Part II: Module SIV - Populations not studied in clinical trials

Not applicable

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Patient exposure for post-marketing use cannot be calculated exactly due to varying dosage, varying duration of treatment and different respectively unknown patient's compliance. Patient exposure can be calculated exactly for clinical trials only, where dosage and duration of treatment is known.

SV.1.1 Method used to calculate exposure

Post-authorisation exposure estimations are calculated using sales data from IQVIA MIDAS. According to the WHO/ATC classification no Defined Daily Dose (DDD) is available for this specific indication of budesonide. The daily dose of 16 mg was defined for budesonide. This DDD is used by the MAH for the calculation of patient-days of Kinpeygo. Patient-years (PY) are calculated by dividing the patient-days by 365.25.

SV.1.2 Exposure

The total volume of Kinpeygo was 38.31 thousand 4-mg-units for the interval 2023-Dec-15 to 2024-Jun-14. Since no daily dose was defined according to WHO/ATC classification for this specific indication of budesonide, and taken into account that one patient takes 16 mg budesonide daily, an exposure of 38,310 patient-days or 104.9 patient-years was calculated.

Table SV.1: Exposure table for last PSUR interval

Country	**Sales volume per country from 2023-Dec-15 to 2024-Jun-14 in thousand 4-mg-units**
Austria	0.70
Croatia	0.40
Czech Republic	0.18
Germany	34.03
Slovenia	0.70
United Kingdom	3.00
Total	**38.31**

Cumulatively, the total exposure of the product according to available data, i.e. starting with PSUR No 1, 2022-Jul-15, is 87,060 patient-days or 238 patient-years.

No pattern of use (evidence of overdose, abuse, misuse, use beyond the recommendations in the RSI, use in special population including, amongst others, use in pregnant or lactating women, or in paediatric or elderly population, or effects of long-term use) of Kinpeygo was identified.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• Use in pregnancy and lactation

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

The reasons for not including an identified or potential risk in the list of safety concerns in the RMP are presented below.

Adverse events not observed in clinical studies conducted with Kinpeygo but included in the SmPC as a standard precaution:

- Hypersensitivity

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

The following risks are well-established side effects with budesonide use and included as potential side effects. However, these effects were not observed in the clinical studies:

- Interaction with potent cytochrome P450 3A4 (CYP3A4) inhibitors
- Risk of adrenal suppression in patients with moderate or severe hepatic impairment

The following risks are well-established side effects associated with glucocorticosteroid use and included as potential class effects. Considering the high first pass metabolism of budesonide resulting in low systemic exposure, no impact on risk benefit balance is anticipated.

- Side effects typical of systemic corticosteroids
- Hypercorticism and adrenal suppression

- Symptoms attributed to withdrawal of steroid therapy (acute adrenal axis suppression, benign intracranial hypertension) or unmasking of allergies after transfer from corticosteroid with high systemic availability
- Increased susceptibility to new infection and increased risk of exacerbation, dissemination, or reactivation of latent infection
- Use in 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 corticosteroids may have unwanted effects.
- Visual disturbance (including cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR))

The following risk is included as general risk for the ingredient sucrose:

- Use in patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks: Not applicable

Important Potential Risks: Not applicable

Missing Information:

Use in pregnancy and lactation

The first diagnosis of IgAN typically occurs during the second and third decades of life. For women this coincides with the child-bearing period (Donadio and Grande 2002). Women with IgAN have similar outcomes to healthy women at early stages of disease if they are normotensive and their preconception GFR exceeds 70ml/min (Abe 1991). Pregnancy complications such as preeclampsia and spontaneous abortion are inversely related to kidney function (Su et al 2017). CKD stages 1 to 4 were classified by eGFR ≥ 90, 60 to 89, 30 to 59, and 15 to 29 mL/min/1.73 m2, according to the KDIGO (Kidney Disease: Improving Global Outcomes) guideline. In this IgAN cohort study, proportions of infant loss in CKD stages 1, 2, and 3 to 4 were 19%, 23%, and 45%, and incidences of severe preeclampsia were 6%, 14%, and 36%, respectively. In multivariable analysis, proteinuria at the beginning of pregnancy and during pregnancy was also a strong risk factor for these adverse pregnancy events (Su et al 2017). The KDIGO 2021 guideline recommends control of glomerular disease and blood pressure prior to planning pregnancy. Kinpeygo is specifically indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN). Hence, patients for which Kinpeygo is indicated have per se an increased risk of adverse pregnancy outcomes. An assessment of the benefit-risk in pregnant women with IgAN would require careful consideration on a case by case basis, and the use of Kinpeygo during pregnancy is expected to be limited.

There are few data describing pregnancy outcomes after oral administration of budesonide in humans. Budesonide was found to cross the placental barrier. The relevance of these observations to humans has not been established. 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 the treatment with Kinpeygo compared to inhaled budesonide. In pregnant animals, budesonide, like other glucocorticosteroids, has been shown to cause

abnormalities of fetal development. The relevance of this to humans has not been established.

According to the data after inhalation of budesonide, budesonide is excreted in human breast milk. One published study reports that budesonide is present in human milk following maternal inhalation of budesonide, which resulted in infant doses approximately 0.3% to 1% of the maternal weight-adjusted dosage and a milk to plasma ratio was approximately 0.5. Budesonide was not detected in plasma of the breastfed infants, and no adverse events were noted in the breastfed infants following maternal use of inhaled budesonide.

Assuming a daily average milk intake of about 150 mL/kg/day and a milk to plasma ratio of 0.5, the estimated oral dose of budesonide for a 5 kg infant is expected to be less than 2 mcg/day for a maternal dose of 16 mg Kinpeygo. Assuming 100% bioavailability in the infant this is about 0.1% of the maternal dose and about 3% of the highest inhaled dose used clinically for asthma in infants.

Due to the lack of clinical study data the use in pregnant or breast-feeding women is included as missing information.

Risk-benefit impact:

Primary IgAN is a serious, progressive disease that leads to decreasing kidney function and progression to ESRD which is associated with a reduced quality of life and shortened life expectancy, and requires haemodialysis or kidney transplantation for survival. Prior to the approval of Kinpeygo, there were no treatments approved for the management of patients with primary IgAN. Standard of care comprises supportive therapy, which focuses on lowering of proteinuria and optimal blood pressure control by maximum tolerated blockade of the renin-angiotensin system (RAS), together with a low sodium diet. When proteinuria persists despite optimal RAS inhibition with Angiotensin Converting Enzyme Inhibitor (ACEI)/ Angiotensin II type I Receptor Blockers (ARBs), patients are at risk of progression to ESRD. The KDIGO 2021 guideline recommends such patients should be considered for enrolment in a clinical trial. Although the clinical benefit of systemic glucocorticosteroid (GCS) therapy has not been established, KDIGO 2021 also suggests patients who remain at a high risk of progressive disease can be considered for a 6-month course of systemic GCS therapy. However, it is noted that the evidence for efficacy is uncertain, and it is emphasised that when systemic corticosteroids are being considered, the important risk of treatment-emergent toxicity must be discussed with patients. Since the KDIGO 2021 guideline was published, the European Medicines Agency (EMA) has granted CMA for Kinpeygo (budesonide) (7/2022), and the US Food and Drug Administration (FDA) has granted accelerated approval to TARPEYO (budesonide) (12/2021) and FILSPARI (sparsentan) (2/2023) for the treatment of patients with primary IgAN; the EC has granted an orphan designation for sparsentan for the treatment of primary IgAN. SGLT2 inhibitors such as dapagliflozin, whilst not specifically indicated for primary IgAN, may also be used in some patients as an additional supportive care measure.

Kinpeygo is a novel oral formulation for targeted release of budesonide. The formulation is designed to release budesonide to the ileum where the Peyer’s patches are concentrated. Mucosal B-cells present in the ileum, including the Peyer’s patches, express glucocorticoid receptors and are responsible for the production of galactose-deficient IgA1 antibodies (Gd-Ag1) causing IgAN. Through their anti-inflammatory and immunosuppressive effects at the glucocorticoid receptor, corticosteroids can modulate B-cell numbers and activity. The efficacy of Kinpeygo has been evaluated and confirmed

in 2 randomised, double-blind, placebo-controlled studies of patients with primary IgAN, who were receiving ReninAngiotensin System (RAS) inhibitor therapy.

Budesonide is a corticosteroid with potent glucocorticoid activity and weak mineralocorticoid activity that undergoes substantial first pass metabolism resulting in a low systemic exposure (10%). In clinical studies Kinpeygo was generally well-tolerated and the safety data were consistent with the known safety profile of budesonide.

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 the treatment with Kinpeygo compared to inhaled budesonide. Non-clinical data show that budesonide crosses the placental barrier and cause abnormalities of fetal development. There are only few data of pregnancy outcomes after oral administration of budesonide in humans. The relevance of this to humans has not been established.

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

In summary, Kinpeygo should be avoided during pregnancy unless there are compelling reasons for therapy with Kinpeygo. The expected benefits for the pregnant woman have to be weighed against the potential risk for the fetus. 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.

Overall, considering the severity and typical course of the disease, the anticipated benefits of Kinpeygo for patients with IgAN as well as the limitation of the use of Kinpeygo to pregnant and/or breast-feeding women when the clinical benefits outweigh the risk for the fetus or the breast-fed infant, the missing information regarding the use during pregnancy and lactation is not considered to negatively impact the benefit-risk profile of Kinpeygo. Data will be collected via a targeted questionnaire on the pregnant patient and the fetus/ born child to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) of the pregnancy as well as any complications occurring in the fetus, the born child and/ or breast-fed child of patients exposed to Kinpeygo.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

There is no need to add new safety concerns or reclassify existing safety concerns within this RMP update; the section is still not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risks: Not applicable, no safety concerns

Important potential risks: Not applicable, no safety concerns

SVII.3.2. Presentation of the missing information

Use in pregnancy and lactation

Evidence source:

The available evidence regarding the use of budesonide in pregnancy and lactation is mainly based on non-clinical data as well as published clinical data related to inhalation of budesonide:

Pregnancy

In pregnant animals, budesonide, like other glucocorticosteroids, has been shown to cause abnormalities of fetal development including cleft palate (Pinsky and Digeorge, 1965, Kusanagi, 1983), intra-uterine growth retardation and congenital malformations, particularly skeletal abnormalities (Kihlström and Lundberg, 1987). The relevance of these observations to humans has not been established. There is no evidence that glucocorticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in humans. However, when administered for prolonged periods or repeatedly during pregnancy, glucocorticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to glucocorticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As stated in Kinpeygo SmPC, Section 4.6, administration during pregnancy should be avoided unless there are compelling reasons for therapy with Kinpeygo and the expected benefits for the pregnant woman have to be weighed against the potential risk for the foetus. Neonates should be carefully observed for signs and symptoms of hypoadrenalism.

Lactation

One study reported that budesonide is excreted in human breast milk following maternal inhalation of budesonide. Maintenance treatment with inhaled budesonide (200 or 400 micrograms twice daily) in asthmatic nursing women resulted in negligible systemic exposure to budesonide in breast-fed infants. In a pharmacokinetic study, the estimated daily dose to infants was 0.3% of the maternal dose for both dose levels, and the mean plasma concentration in infants was estimated to be 1/600 of the concentrations observed in maternal plasma, assuming complete oral bioavailability in the infant (Fält et al., 2007). Budesonide concentrations in infant plasma samples were less than the limit of quantification. Based on data about inhaled budesonide and the fact that budesonide exhibits linear pharmacokinetic characteristics within the therapeutic dose ranges following inhaled, oral or rectal administration, exposure of the breast-fed infant to budesonide is expected to be low at therapeutic doses of Kinpeygo. Assuming a daily average milk intake of about 150 mL/kg/day and a milk to plasma ratio of 0.5, the estimated oral dose of budesonide for a 5 kg infant is expected to be less than 2 mcg/day for a maternal dose of 16 mg Kinpeygo. Assuming 100% bioavailability in the infant this is about 0.1 % of the maternal dose and about 3% of the highest inhaled dose used clinically for asthma in infants. However, the 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.

Conclusion:

Overall, the safety profile of budesonide is well-established. According to the SmPC, Kinpeygo administration should be avoided during pregnancy unless there are compelling reasons for therapy with Kinpeygo. The expected benefits for the pregnant woman have to be weighed against the potential risk for the fetus. Furthermore, according to the SmPC, 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.

Hence, the use during pregnancy must be made on a case by case basis at the discretion of the treating physician, weighing the expected benefits for the pregnant/ breast-feeding woman against the potential risk for the fetus/ breast-fed child. A targeted questionnaire will be used to obtain follow-up information for all pregnancy case reports or case reports involving a patient who has breast-fed a child (see Section III.3 and Annex 4). Data will be collected whenever possible on the pregnant patient and the fetus who will be closely followed-up throughout the duration of the pregnancy to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) of the pregnancy as well as any complications occurring the fetus, the born child and/ or breast-fed child of patients exposed to Kinpeygo.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• Use in pregnancy and lactation

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

The proposed Pharmacovigilance Plan consists of routine pharmacovigilance activities, including the collection, assessment and processing of individual case safety reports (ICSRs) and ongoing safety surveillance and periodic signal detection.

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities will include the collection, assessment and processing of ICSRs and ongoing safety surveillance and periodic signal detection.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are considered necessary to address the safety concerns:

Specific adverse reaction follow-up questionnaire for missing information "Use in pregnancy and lactation"

- Targeted Pregnancy/ Breast-feeding follow-up questionnaire (see Annex 4): The purpose of the targeted questionnaire is to closely follow-up events in pregnant/ breast-feeding women as well as the fetus/ born child and/or breast-fed child influding but not limited to spontaneous miscarriage, elective termination, normal birth, or congenital abnormality of patient exposed to Kinpeygo during pregnancy

and breast-feeding as well as any complications occurring in the fetus, the born child and/ or breast-fed child of patients exposed to Kinpeygo.

Other forms of routine pharmacovigilance activities for missing information "Use in pregnancy and lactation"

- cumulative review of case reports on the use of Kinpeygo in pregnancy and lactation, which will be included in the PSUR.

III.2 Additional pharmacovigilance activities

None proposed.

III.3 Summary table of additional pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product Entocort. The marketing authorisation applicant considers routine risk minimisation activities as sufficient.

V.1 Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Missing Information	
Use in pregnancy and lactation	Routine risk communication: • SmPC section 4.6, 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: Legal status: • Prescription only medicinal product

V.2 Additional risk minimisation measures

No additional risk minimization measures are deemed necessary. For further information please also refer to section SVII.3.2.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing Information		
Use in pregnancy and lactation	Routine risk minimisation measures: • SmPC section 4.6, 5.3 • Legal status: Prescription only medicinal product Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted Pregnancy/ Breast-feeding follow-up Questionnaire • Cumulative review of case reports on the use of Kinpeygo in pregnancy and lactation will be included in the PSUR. Additional pharmacovigilance activities: • None

Part VI: Summary of the risk management plan

Summary of risk management plan for Kinpeygo (budesonide)

This is a summary of the RMP for Kinpeygo. The RMP describes important risks of Kinpeygo and uncertainties (missing information).
Kinpeygo's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Kinpeygo should be used.
This summary of the RMP for Kinpeygo should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).
Important new concerns or changes to the current ones will be included in updates of Kinpeygo's RMP.

I. The medicine and what it is used for

Kinpeygo is authorized for the treatment of adults with primary IgAN with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.8 g/g) (see SmPC for the full indication). It contains budesonide as the active substance and it is given orally.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Kinpeygo, together with measures to minimise such risks and the proposed studies for learning more about Kinpeygo's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Reports (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Kinpeygo is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Kinpeygo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Kinpeygo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• Use in pregnancy and lactation

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• Use in pregnancy and lactation
Risk minimisation measures	Routine risk minimisation measures: – SmPC section 4.6, 5.3 – Legal status: Prescription only medicinal product Additional risk minimisation measures: – None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no ongoing or planned studies which are conditions of the marketing authorisation or specific obligation of Kinpeygo.

II.C.2 Other studies in post-authorisation development plan

There are no other studies required for Kinpeygo.

Part VII: Annexes

Table of contents

Annex 4 Specific adverse drug reaction follow-up forms

Targeted Pregnancy/ Breast-feeding follow-up Questionnaire

KINPEYGO (Budesonide) – PREGNANCY/ BREAST-FEEDING TARGETED QUESTIONNAIRE
Request for Additional Information

Reporter

Who is providing this report: ☐ Mother ☐ Father
☐ Healthcare Provider, please specify specialty: .....
☐ Other, please specify: .....

Please provide **contact information** for the reporter at the end of this form.

Patient and Treatment Information

Who of the parents received Kinpeygo (budesonide): ☐ Mother ☐ Father

Parent	Age (years)	Weight	Height	Profession
Mother		_____ ☐ kg	_____ ☐ cm	
Father (unknown ☐)		_____ ☐ kg	_____ ☐ cm	

Trade name/ INN	Daily dose (unit)	Mode of application	Indication/ Date of diagnosis	Therapy dates (from – to)
KINPEYGO		☐ Oral ☐ Other, please specify: _____	☐ IgAN ☐ Other, please specify: _____ Date of diagnosis: _____ (dd-mmm-yyyy)	Therapy first started: Therapy stopped:
	Please list all periods of treatment interruptions as applicable:			

Current Pregnancy

First day of last menstruation: ..... Estimated date of conception: .....

Expected date of delivery: .....

Week of gestation at the time of reporting: .....OR

Outcome of pregnancy:
☐ full term, date of delivery
☐ premature birth, date of delivery: ..... gestational age: .....
☐ spontaneous miscarriage gestational age: .....
☐ elective termination gestational age: .....
Medical reason for elective termination: ☐ No ☐ Yes, please specify: .....

KINPEYGO (Budesonide) – PREGNANCY/ BREAST-FEEDING TARGETED QUESTIONNAIRE
Request for Additional Information

Course of Pregnancy

Prenatal examinations	Date	Normal	Abnormal	if abnormal, please specify
Amniocentesis				
Testing of alpha-foetoproteins				
Chorionic villus sampling (CVS)				
Ultrasound (US): 1st US: 2nd US: 3rd US:				 ....
Genetic Screening				

Regular **preventive medical checkups:** ☐ yes ☐ no ☐ unknown

Potential risks (drugs, smoking, alcohol, x-ray examinations etc.) and **complications,** like e.g. hospitalisation, infections during pregnancy etc.):

☐ yes ☐ no ☐ unknown
if yes, please specify: .....

.....

Pre-eclampsia: ☐ yes ☐ no
Eclampsia: ☐ yes ☐ no
Uncontrolled hypertension: ☐ yes ☐ no
Infections: ☐ yes ☐ no

IgAN Status (renal function during pregnancy):

At time of conception:	GFR*:	UPCR**:.....	Comment: .....
1st trimester:	GFR*:	UPCR**:.....	Comment: .....
2nd trimester:	GFR*:	UPCR**:.....	Comment: .....
3rd trimester:	GFR*:	UPCR**:.....	Comment: .....

*GFR: Glomerular Filtration Rate **UPCR = Urine Protein-to-Creatinine Ratio

Medical History and Concomitant Medication at time of Conception and during Pregnancy

Previous Pregnancies:

Number of **previous** pregnancies:	
Healthy children (no birth defect):	
Children with birth defect: genetic birth defect ☐ yes ☐ no ☐ unknown if yes, please describe birth defect:	
Induced abortions:	
Spontaneous abortions:	
Stillbirths:	

Hereditary diseases, malformations, chronic diseases of expectant parents and in their families:

☐ yes ☐ no ☐ unknown, if yes, please specify:
.....

KINPEYGO (Budesonide) – PREGNANCY/ BREAST-FEEDING TARGETED QUESTIONNAIRE
Request for Additional Information

Concomitant Medication: Please include all concomitant medication including e.g. hypertensive treatment, folic acid prophylaxis, iron supplementation etc.

Trade name/ generic name (INN*)	Daily dose (unit)	Mode of application	Indication	Therapy dates (from – to)

*INN= International nonproprietary name

Data Concerning Childbirth and Child

Child	Sex	APGAR score			Circumference of the head	Birth weight and height		Foetal lie	Outcome*	Abnormity	
	m/ f	1	5	10	cm	kg	cm			yes	no
1											
2											
3											

*Outcome:
1. Live-birth,
2. Spontaneous abortion (up to 20th week),
3. Stillbirth (20th – 27th week)
4. Stillbirth (from 28th week)
5. Induced abortion
6. Death of mother and child
7. Ectopic pregnancy, e. g. tubal pregnancy

Were there any **complications during childbirth?** ☐ yes ☐ no ☐ unknown, please specify
Does the child have any **congenital malformations?** ☐ yes ☐ no ☐ unknown, please specify
(please also specify in case of induced or spontaneous abortions, stillbirth or death of neonate)

.....

.....

Breast-feeding

Mother is/was breast-feeding? ☐ yes ☐ no* ☐ unknown ☐ not applicable

*If patient is/has not breast-feeding, please provide reason: ☐ medical reason, please specify: .....
☐ personal reason

Did the mother or breast-fed child experience any complications during breast-feeding?

Mother: ☐ unknown ☐ no ☐ yes, please specify: .....

.....

Breast-fed child: ☐ unknown ☐ no ☐ yes, please specify: .....

.....

Who can be contacted for further information?

Name: **Function (e.g. Gynaecologist):**	**Street**
Postal code / City	**Telephone**

KINPEYGO (Budesonide) – PREGNANCY/ BREAST-FEEDING TARGETED QUESTIONNAIRE
Request for Additional Information

Further comments:

.....

.....

.....

Name/ Adress/ Contact details of Reporter	**Please return the completed form to:**
Date **Signature (Reporter)**	

Comment / Assessment from Healthcare Provider

This section should only be filled out if the reporter is a healthcare provider

If pregnancy was terminated early, or if any complications occurred during childbirth or with the neonate:

In your view, is there reasonable evidence that these events are to be attributed to the drug exposure during pregnancy?

☐ yes ☐ no, ☐ not assessable; please explain (please add diagnostic findings if applicable):

.....

.....

If the child experienced any complications during breast-feeding:

In your view, is there reasonable evidence that these events are to be attributed to the drug exposure during breast-feeding?

☐ yes ☐ no, ☐ not assessable; please explain (please add diagnostic findings if applicable):

.....

.....

Thank you very much for your cooperation!

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Not applicable

Annex 7 Other supporting data (including referenced material)

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