EU RISK MANAGEMENT PLAN FOR CELLCEPT® / MYCOPHENOLATE MOFETIL

RMP version to be assessed as part of this application: 2.0

RMP Version number: 2.0

Data lock point for this RMP: 15 January 2026

Date of final sign off: See electronic signature on the last page of this document

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Rationale for Submitting an Updated RMP

European Union Risk Management Plan (EU RMP) Version 2.0 is being prepared in response to PBRER assessment report PSUSA/00010550/202505 dated 15 January 2026 to remove the missing information " Long term safety (growth retardation, pubertal maturation and fertility, bone health, metabolic problems and neurocognitive development)" and removal of guided questionnaires for patients and health care providers reporting CellCept exposure during pregnancy.

Summary of Significant Changes in This RMP

Part I Product overview updated with dosage in the European Economic Area (EEA) as per updated European Union Summary of Product Characteristics (EU SmPC)

Part II: Module SV - Post-authorization experience updated with data from the latest PBRER DLP of 2 May 2025.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP updated with rationale for removal of the missing information.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information updated with removal of the missing information

Part II: Module SVIII - Summary of the Safety Concerns updated.

Part III.1 Routine Pharmacovigilance Activities updated with removal of questionnaires for patients and health care professionals

Part V: Risk Minimization Measures (Including Evaluation Of The Effectiveness Of Risk Minimization Activities) updated with removal of details related to missing information.

V.3 Summary Of Risk Minimization Measures updated with removal of missing information

Annex 4 updated with removal of questionnaires for patients and health care professionals

Annex 7 updated with information on post-authorization use in populations not studied in clinical trials, specifically Pregnant and Breastfeeding Women in line with the latest periodic benefit risk evaluation report (PBRER) with data lock point (DLP) 2 May 2025

Annex 8: Updated with changes made to this version of the RMP

Other RMP Versions under Evaluation

Not applicable

Details of Currently Approved RMP

RMP Version Number: 1.2

Approved with Procedure Number EMEA/H/C/000082/II/0170/G

Date of approval (opinion date):14 November 2024

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product(s) Overview

Active Substance(s) (INN or common name)	Mycophenolate mofetil
Pharmacotherapeutic group(s) (ATC Code)	L04AA06
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	CellCept®
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Selective Immunosuppressive agent
	Summary of mode of action: Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA is a selective, uncompetitive and reversible inhibitor of IMPDH, and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines whereas other cell types can utilise salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells. In addition to its inhibition of IMPDH and the resulting deprivation of lymphocytes, MPA also influences cellular checkpoints responsible for metabolic programming of lymphocytes. It has been shown, using human CD4+ T-cells, that MPA shifts transcriptional activities in lymphocytes from a proliferative state to catabolic processes relevant to metabolism and survival leading to an anergic state of T-cells, whereby the cells become unresponsive to their specific antigen
	Summary of Composition:

Active Substance(s) (INN or common name)	Mycophenolate mofetil
	mycophenolate mofetil (MMF) is available as a sterile powder to be reconstituted and diluted prior to intravenous (IV) administration. MMF is available for oral (PO) administration as 250 mg hard gelatin capsules, 500 mg film-coated tablets, and a powder for oral suspension (1 g MMF in 5 mL of the constituted suspension).
Hyperlink to the Product Information	Refer to EU Product Information
Indication(s) in the EEA	Current: CellCept is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in *adult and paediatric (1 to 18 years of age)* patients receiving allogeneic renal, cardiac or hepatic transplants.
	Proposed: NA
Dosage in the EEA	Current: *Adults* *Renal transplant* Treatment should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1 g administered twice daily (2 g daily dose). *Cardiac transplant* Treatment should be initiated within 5 days following transplantation. The recommended dose in cardiac transplant patients is 1.5 g administered twice daily (3 g daily dose). *Hepatic transplant* Treatment of intravenous mycophenolate mofetil should be administered for the first 4 days following hepatic transplant, with oral mycophenolate mofetil initiated as soon after this as it can be tolerated. The recommended oral dose in hepatic transplant patients is 1.5 g administered twice daily (3 g daily dose). *Paediatric population (1 to 18 years)* The paediatric dosing information in this section applies to all oral formulations within the range of mycophenolate mofetil products, as appropriate. Different oral formulations should not be substituted without clinical supervision.

Active Substance(s) (INN or common name)	Mycophenolate mofetil
	The recommended mycophenolate mofetil initial dose for paediatric renal, cardiac and hepatic transplant patients is 600 mg/m^2 (of body surface area (BSA)), administered orally, twice daily (initial total daily dose not to exceed 2 g, or 10 ml of the oral suspension). The dose and product form should be individualised based on clinical assessment. If the recommended initial dose is well tolerated but does not achieve clinically adequate immunosuppression in paediatric cardiac and hepatic transplant patients, the dose can be increased to 900 mg/m2 BSA twice daily (maximum total daily dose of 3 g, or 15 ml of the oral suspension). The recommended maintenance dose for paediatric renal transplant patients remains at 600 mg/m2 twice daily (maximum total daily dose of 2 g or 10 ml of the oral suspension). The mycophenolate mofetil powder for oral suspension should be used in those patients unable to swallow capsules and tablets and/or with a BSA lower than 1.25 m2 due to the increased risk of choking. Patients with a BSA of 1.25 to 1.5 m2 may be prescribed mycophenolate mofetil capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a BSA greater than 1.5 m2 may be prescribed mycophenolate mofetil capsules or tablets at a dose of 1 g twice daily (2 g daily dose). As some adverse reactions occur with greater frequency in this age group (see section 4.8) compared with adults, temporary dose reduction or interruption may be required; these will need to take into account relevant clinical factors including severity of reaction.
	Proposed: NA
Pharmaceutical form(s) and strengths	Current: Oral administration: CellCept is supplied as hard capsules, film-coated tablets, and powder for oral suspension. Each capsule contains 250 mg MMF; each tablet contains 500 mg MMF; 5 mL of the reconstituted suspension contains 1 g of MMF.

Active Substance(s) (INN or common name)	Mycophenolate mofetil
	Intravenous administration: CellCept is supplied in single-use vials as white to off-white powder for solution for infusion. Each vial contains the equivalent of 500 mg MMF (as the hydrochloride salt).
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the European Union?	No

BSA = body surface area; EEA = European Economic Area; IMPDH = inosine monophosphate dehydrogenase; INN = International non-proprietary name; IMP = investigational medicinal product; IV = intravenous; MMF = mycophenolate mofetil; MPA = mycophenolic acid; RMP = Risk Management Plan.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
A2ALL	Adult-to-Adult Living Donor Liver Transplantation Cohort Study
ABMR	antibody mediated rejection
ACR	acute cellular rejection
AE	adverse event
ANZDATA	Australian and New Zealand Dialysis And Transplant
ATG	anti-thymocyte globulins
AUC	area under the plasma concentration-time curve
AZA	Azathioprine
BPAR	biopsy proven acute rejection
CHD	congenital heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COPA	controlling profitability analysis
DSR	drug safety report
E.U. RMP	E.U. Risk Management Plan
EEA	European Economic Area
ELTR	European Liver Transplant Registry
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	food and drug administration
HCPs	healthcare providers
HCUP	healthcare cost and utilization project
HES	hospital episode statistics
HR	hazard ratio
HT	heart transplant
IBD	international birth date
IQR	interquartile range
ISHLT	international society for heart and lung transplantation
IV	Intravenous
IVIG	IV immunoglobulins
KPE	kasai portoenterostomy
LT	liver transplant
MAA	marketing authorization application
MAH	marketing authorization holder

Abbreviation	Definition
MPA	mycophenolic acid
NAPRTCS	North American paediatric renal trials and collaborative studies special study
NIS	nationwide inpatient sample
NYS	New York State
OPTN	organ procurement and transplantation network
PHTS	paediatric heart transplant study
PAM	post-authorization measures
PLT	paediatric liver transplant
PSURs	periodic safety update reports
PV	Pharmacovigilance
RMP	risk management plan
RoW	rest of world
SmPC	summary of product characteristics
SRTR	scientific registry of transplant recipients
UNOS	united network for organ sharing
USA	United States of America

PART II: SAFETY SPECIFICATION

PART II: MODULE SI— EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 GRAFT REJECTION IN ALLOGENIC CARDIAC TRANSPLANT POPULATION

Incidence

Adult Patients

A retrospective analysis using data collected from the United Network for Organ Sharing (UNOS) was performed on 34,361 adult patients who received a heart transplant (HT) in the USA between 2000 and 2017 and received induction therapy with T cell depleting agents. At one year, there were a total of 6,591 patient reported rejection events among 26,356 heart transplants recipients accounting for the incidence of 25%; 95% confidence interval [CI] (24.5-25.5) (Bellumkonda et al. 2022).

The study using data from Scientific Registry of Transplant Recipients (SRTR) included 5160 African American HT patients from 1 January 2008, and 31 December 2018. The HT patients were divided into two groups; one who received the induction immunosuppression therapy (n=2787; 54%) and those who did not (n=2373; 46%). The overall Incident cases of acute rejection occurred in 2239 patients (43.4%) with 984 patients (41.4%) who were not prescribed induction and 1255 patients (45%) who were prescribed induction immunosuppression (Salia et al. 2022).

Paediatric Patients

In the USA, a retrospective study was conducted on 176 paediatric patients who underwent their first orthotopic HT between 2013 and 2021. The mean age of the recipients at the time of transplant was 9.8±7.2 years. The incidence of acute cellular rejection before and after one year of HT was 23.9% and 15.3%, respectively (Armstrong et al. 2024). The Paediatric Heart Transplant Study (PHTS) database included 3985 patients from 56 different centers who underwent their first HT between 2010 and 2019. Among the included patients, 873 (21.9%) experienced acute rejection within the first-year post-transplant (Godown et al. 2021). A total of 3259 paediatric HT recipients between January 2005 and December 2015 in the PHTS database were identified. Rejection with severe hemodynamic compromise developed in 309 patients (9.5%) at a median of 1.2 years post-transplant (Kleinmahon et al. 2019). In a multi−institutional study, 2227 patients who received HT allografts between 1993 and 2006 at 36 centers across the USA in the PHTS were identified. Within five years of HT, 541 (25%) had at least one incident of rejection with hemodynamic compromise. Among these, the initial episode of rejection was classified as rejection with mild hemodynamic compromise in 350 patients (65%) and rejection with severe hemodynamic compromise in 191 patients (35%) (Everitt et al. 2011).

Data from UNOS and Paediatric Health Information System identified 4803 children (<18 years) undergoing first-time HT between 2003 and 2022 with diagnoses of heterotaxy (n=278), other-congenital heart disease (CHD) (n=2236), and non-CHD cardiomyopathy (n=2289). The frequency of acute graft rejection was 15%, 17% and 11% during index hospitalization, and 29%, 30%, and 23% after one year in heterotaxy, other CHD and non-CHD cardiomyopathy paediatric HT patients respectively (Greenberg et al. 2023).

Prevalence

Adult Patients

A study utilizing the Healthcare Cost and Utilization Project (HCUP)-Nationwide Inpatient Sample (NIS) data set included 30,016 hospitalizations of HT recipients between 1999 and 2014 in the USA, among which 1,953 (6.5%) suffered from sudden cardiac arrest. Overall, 8732 patients had a graft rejection accounting for prevalence of 29.1%; 95% CI (28.6-29.6) (Isath et al. 2022).

An observational, prospective, multicenter study conducted in 35 heart transplant centers across United States called Outcomes AlloMap Registry started in March 2013 included 1504 cardiac transplant patients. The prevalence of moderate to severe acute cellular rejection (ACR) (≥2R) was 1.7% (19 of 1,118) before 6 months and 2.2% (30 of 1,338) after 6 months (Moayedi et al. 2019).

Paediatric Patients

Paediatric heart transplant accounts for approximately 14% of the total heart transplants worldwide (Dipchand et al. 2013). The number of paediatric heart transplants reported to the International Society for Heart and Lung Transplantation (ISHLT) registry has increased over time to 442 in 2004, 586 in 2014, and 684 in 2015 (Rossano et al. 2016). In 2019, there were 507 paediatric heart transplants performed in the USA (14%), in patients up to 17 years of age (Kwong et al. 2020).

Demographics

Adult Patients

In a retrospective analysis using data from the UNOS including 34,361 HT recipients from the USA between 2000 and 2017, the median age of the recipients was 55 years (interquartile range [IQR]: 46-62) with 25% female population (Bellumkonda et al. 2022).

In a study utilizing the HCUP-NIS data set that included 30,016 hospitalizations of HT recipients between 1999 and 2014 in the USA, the median age was 55 (IQR: 45-62). Most patients in the study were men (74.14%%) and White (57.87%) (Isath et al. 2022).

Paediatric Patients

A study from USA using the PTHS database (1993-2004) included paediatric 1886 HT patients. The patients were analyzed by era - the early era was defined as children listed for HT from 1 January 1993 to 31 December 2004; middle era from 1 January 2005 to 31 December 2009; and recent era from 1 January 2010 to 31 December 2019. The median age at the time of transplantation varied across the eras: 2.88 years (0.38–2.2) for the early era, 3.9 years (0.65–12.4) for the middle era, and 4.86 years (0.74–13.06) for the recent era. It was observed that the median age at the time of transplantation has gradually increased over the three eras, with the recent era having the highest median age (4.86 years) (Richmond et al. 2024). In the PHTS database, the median age of paediatric HT patients transplanted between 2010 and 2019 was found to be 4.8 years (IQR: 0.7–13.1) with 45% females (Godown et al. 2021).

The Main Existing Treatment Options

Adult Patients

Following solid organ transplantation, immunosuppression aims at preventing graft rejection and reducing undesirable side effects like infection, cancer, and drug toxicity. A combination of immunosuppressive drugs with various mechanisms of action is employed to accomplish this at relatively low doses. Immunosuppressive therapy is generally categorized into 3 stages: induction, maintenance, and treatment of rejection. The “triple-drug” approach is the cornerstone of modern maintenance immunosuppressive regimens that consist of a calcineurin inhibitor, an antiproliferative drug, and corticosteroids.

The most frequently prescribed combination of medications is tacrolimus, mycophenolate mofetil, and prednisone.

In some patients, an antibody induction might be employed at the time of transplant in addition to the maintenance immunosuppression. When compared to no induction at all, antibody induction therapy has been found to reduce rejection rates and enhance long-term patient and graft survival outcomes (Jasiak et al. 2016).

Antibody Induction

Except for liver transplant (LT), induction therapy with antibodies is increasingly being used in most solid organ transplants. The most often utilized antibodies for induction therapy are basiliximab, alemtuzumab, and rabbit Anti-thymocyte globulins (ATG).

The use of induction immunosuppression in LT remains controversial. In a retrospective cohort study of adult, first-time liver alone recipients (N=69,349) at 114 USA centers between 2005–2018 using data from the United Network for Organ Sharing, 27% of recipients received either non-depleting or depleting induction. Non-depleting induction included the interleukin-2 receptor antagonists daclizumab and basiliximab. Depleting

induction included thymoglobulin, alemtuzumab and rituximab. Non-depleting and depleting induction were associated with a lower risk of death/graft failure compared to no induction, however the absolute incremental benefits of induction over no induction were small (Bittermann et al. 2019).

Maintenance immunosuppression

Corticosteroids: The oldest component of the triple-drug regimen, corticosteroids are used in induction, maintenance, and rejection procedures. The entire process of immune activation, including antigen presentation by antigen-presenting cells, cytokine release, including but not limited to interleukins (such as IL-1, IL-2, and IL-6) and tumour necrosis factor, and subsequently lymphocyte proliferation, is affected by their immunosuppressive effects.

Calcineurin inhibitors (tacrolimus and cyclosporin): Nuclear factor of activated T cells, a necessary transcription factor in the production of cytokines by T cells, is dephosphorylated by the phosphatase calcineurin. Tacrolimus (as tacrolimus-FKBP12 complex) and cyclosporin (as cyclosporin cyclophilin complex) inhibit calcineurin, which prevents the production of IL-2, the cytokine that triggers lymphocyte activation (Jasiak et al. 2016).

Antiproliferative agents (azathioprine, mycophenolate mofetil, and mycophenolate sodium)

Azathioprine

Azathioprine is uncommonly used in solid-organ transplantation due to the availability of more effective and generally better-tolerated products such as mycophenolate. However, it may be used in selected cases, for example to avoid the teratogenic risk of mycophenolate in patients who wish to become pregnant.

Mycophenolic acid derivatives

Mycophenolate mofetil (CellCept) is converted to mycophenolic acid (MPA) in vivo, while mycophenolate sodium (Myfortic) is the sodium salt of MPA. MPA is a specific inhibitor of inosine monophosphate dehydrogenase, a necessary enzyme for the de novo production of purines. As a result, lymphocyte proliferation is specifically inhibited by MPA derivatives because these cells are unable to use purine synthesis salvage mechanisms.

mTOR inhibitors (sirolimus and everolimus)

Everolimus (Zortress) and sirolimus (Rapamune) stop the cell cycle in the G1-S phase to prevent lymphocyte proliferation. Their main clinical benefit is the ability to spare calcineurin inhibitors.

Co-stimulation blocker

Belatacept

Belatacept blocks CD86-mediated co-stimulation and prevents T cells from producing cytokines. It is the first intravenous maintenance immunosuppressant that the Food and Drug Administration (FDA) has approved, and it has the advantage of not requiring therapeutic drug monitoring. Belatacept regimen demonstrated equivalent patient and graft survival and better renal function when compared to cyclosporin-based maintenance immunosuppression in recipients of typical criteria donor kidney transplants receiving basiliximab induction, mycophenolate mofetil, and corticosteroids (Jasiak et al. 2016).

TREATMENT OF REJECTION

Steroid pulses and ATGs

To treat T-cell mediated reaction and antibody mediated rejection (ABMR) episodes, high intravenous (IV) corticosteroid dosages (such as methylprednisolone 250–1000 mg each dose) are given over a few days. This course of therapy is frequently referred to as “steroid pulse”.

Rituximab

Rituximab, a monoclonal antibody, binds to the CD20 antigen on B cells and triggers complement-mediated cytotoxicity in B lymphocytes. In conjunction with plasmapheresis and IV immunoglobulins (IVIG), it is largely utilized in transplant for desensitization and treatment of ABMR. Patients should take acetaminophen and diphenhydramine premedication’s before receiving rituximab infusion. The initial infusion rate should be 50 mg/h; however, the infusion rate can be raised by 50 mg/h every 30 minutes.

Intravenous immunoglobulin

A range of immunological indications have been treated with IVIG products, which are made from pooled human plasma. They are generally utilized in solid-organ transplantation as desensitization, ABMR therapy, and post plasmapheresis IgG replacement medicines. There are 3 main effects on immune cell function that are related to how they desensitize patients or treat rejection. This includes apoptosis induction in B cells, a decrease in T cell activation, and an inhibition of complement activity (Jasiak et al. 2016).

Paediatric Patients

The treatment for solid organ transplantation rejection (heart, kidney and liver) among paediatric patients is similar to the treatment in adult patients, however the dosages vary depending on age or body surface area.

Risk Factors for the Rejection

Adult Patients

Younger age, female sex, greater degrees of human leukocyte antigen (HLA) mismatch (4 or more HLA mismatches), African American race, panel-reactive groups ≥25%, and presence of ventricular assisted device at the time of transplant were associated with increased risk of treated rejection at 1 year (Bellumkonda et al. 2022).

A study including 396 patients who underwent orthotopic heart transplantation in Prague between January 2005 and December 2015 reported that carriers of transplanted hearts with the fat mass and obesity related-gene genotype exhibited a significantly increased risk of suffering from both types of rejection in comparison to carriers of hearts with at least one G allele [OR: 2.6; 95% CI (1.15–5.7)] (Hubacek et al. 2018).

Paediatric Patients

Age more than 10 years with hazard ratio [hazard ratio [HR]: 2.65; 95% CI, (1.16–6.08)], non-white race [HR: 1.63; 95% CI (1.21–2.19)], and non-A blood group [HR: 1.39; 95% CI (1.02–1.90)] were found to be significant predictors of rejection with severe hemodynamic compromise (Everitt et al. 2011).

Rejection with severe hemodynamic compromise among paediatric HT recipients was associated with age at HT 1-5 years vs <1 year [HR: 1.51; 95% CI (1.04–2.18)], age more than 10 years vs less than 1 year [HR: 1.83; 95% CI (1.29–2.60)], recipient race black [HR:1.64; 95% CI (1.25−2.15)], prior cardiac surgery [HR: 1.55; 95% CI (1.03–2.31)], recipient on inotropes, pressors, or thyroid hormones at transplant [HR: 1.45; 95% CI (1.09-1.94)], ventricular assisted device support at transplant [HR: 1.65; 95% CI (1.18-2.29)], and maintenance steroids [HR: 1.39; 95% CI (1.06–1.82)] (Kleinmahon et al. 2019).

Natural History of the Indicated Condition in the (Untreated) Population

Adult Patients

If the transplant recipient already has alloantibodies, hyperacute rejections happen within the first few minutes to hours following transplantation. These antibodies are directed against the major histocompatibility complex or ABO blood group antigens that invade the allograft and draw in inflammatory cells that cause platelet aggregation and tissue necrosis. Hyperacute rejection caused by antibodies that are reactive to the HLA is relatively uncommon because of modern crossmatching procedures. In the days to

months following the transplant, acute rejection may happen. Allo-reactive T cells and alloantibodies both play a role in this type of rejection. By cytotoxic processes, allo-reactive CD8+ T cells directly assault and kill the transplanted organ. Furthermore, alloantibodies also contribute to the rejection. These alloantigen-specific antibodies cause complement activation and neutrophil recruitment, which results in thrombotic ischemia of the transplanted organ (Stolp et al. 2019).

A retrospective analysis of data from the International Society for Heart and Lung Transplantation included 85,647 adult patients who underwent HT between January 1985 and December 2010. Among them 1,851 (2.2%) had transplantation for adult congenital heart disease (ACHD). For all adults undergoing HT, the most common causes of death in the first year were graft failure (29%), infection (22%), multi-organ failure (12%) and acute rejection (10%). Factors associated with reduced survival after HT in the general adult population and observed in the ACHD study cohort included a greater likelihood of pre-HT ventilation and higher rates of allo-sensitization (defined as panel-reactive antibodies $>$10%) (Burchill et al. 2014).

Paediatric Patients

Data from UNOS and the Paediatric Health Information System comprising 4803 children ($<$18 years) undergoing first-time HT between 2003 and 2022, indicated that the mortality due to graft failure/rejection was 31% among heterotaxy patients, 32% among other CHD group patients and 30% in cardiomyopathy patients (Greenberg et al. 2023). A multi-institutional study of 2227 patients who received allografts between 1993 and 2006 at 36 centers in the PHTS estimated 30% deaths caused by acute rejection during the time-period of 1993-1999 and 42.1% deaths between 2000 and 2006 (Everitt et al. 2011).

Important Co-Morbidities

Adult Patients

A study utilizing the HCUP-NIS data set included 30,016 hospitalizations of HT recipients between 1999 and 2014 in the USA. The most common co-morbidities were diabetes mellitus (22.7%), hypertension (21.8%), hyperlipidemia (20.8%), renal failure (20.0%), thyroid disorders (11.3%) and hypokalemia (8.8%) (Isath et al. 2022).

Paediatric Patients

Khan et al. 2023., utilized the Retrospective United Network of Organ Sharing database study of paediatric patients listed for heart transplant between 2005 and 2019 with Lansky Play Performance Scale (LPPS) scores at listing to identify risk factors in paediatric patients while on waiting lists for organ transplantation.

There were 4169 patients identified and their functional status was strongly associated with waitlist and post-transplant outcomes. The authors conclude that Interventions targeting functional impairment may improve paediatric heart transplantation outcomes. This suggests that risk factors in paediatric patients are associated with the impaired organ itself, rather than co-morbidities.

SI.2 GRAFT REJECTION IN ALLOGENIC HEPATIC TRANSPLANT POPULATION

Incidence

Adult Patients

A systemic review of studies comparing various immunosuppressive regimens from January 2007 to September 2015 showed wide variability of reported ACR incidence in LT recipients from 34 randomized controlled trials ranging from 5% (Tacrolimus, mycophenolate, anti-interleukin-2 and steroids) to 66.7% (Antithymocyte globulin + weaning Tacrolimus) (Rodríguez-Perálvarez et al. 2016).

Another systematic review and meta-analysis of nine observational studies reported the incidence of late acute rejection ranging from 7%-40% in LT patients (Nacif et al. 2015).

A retrospective case-control study using data from the Organ Procurement and Transplantation Network (OPTN) conducted from 2000-2011 including 40,593 primary LT recipients with Hepatitis B virus, hepatitis C, steatohepatitis, and immune liver disease. A total of 8425 (21%) had at least one ACR episode over a period of 10 years (Veerappan et al. 2016).

A data analysis from two cohorts; one Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) that included 890 LT recipients from 2003 through 2014 and another cohort SRTR) included 45,423 LT recipients from 2005-2013. Among all 890 A2ALL LT recipients, 239 (26.9%) had $\geq$1 episode of biopsy proven acute rejection (BPAR) at a median 49-day post-LT. Among 45,423 LT recipients, 7066 (15.6%) had $\geq$1 episode of BPAR at a median 88.6-day post-LT (Levitsky et al. 2017).

Paediatric Patients

In Europe, the ChilSFree study observed 246 children who underwent de novo isolated LT between December 2012 and October 2016. During the first-year post-transplantation, it was observed that 82 patients experienced at least one biopsy-proven rejection, resulting in an incidence of 33.3% (Goldschmidt et al. 2024). The data of 2032 paediatric liver transplant (PLT) recipients who underwent surgery in China between 2006 and 2019 were retrospectively analyzed. Among 2032 PLT recipients, 1687 recipients underwent an immunosuppression (IS) protocol without switching to other IS drugs, while 345 recipients switched to other IS drugs. The overall incidence of acute rejection in liver transplant recipients, regardless of the treatment cohorts, was 27.3% within three months after transplantation. It was observed that patients in the switching

IS drugs group had a higher rate of acute rejection within 3 months after LT and a higher rate of developing mental, neurological, and urinary complications after LT (Gu et al. 2023). A retrospective cohort study of 2216 PLT recipients between 1 January 2006 to 31 May 2017 using UNOS data was identified. The median unadjusted rate of acute rejection after one year of transplant was 36.92% (IQR, 22.36%-44.52%) (Kanneganti et al. 2022). Another retrospective study included 640 Chinese PLT patients (aged ≤14 years) between January 2016 and December 2019. A total of 104 patients experienced late-onset acute cellular rejection resulting an incidence of 16.3% (Si et al. 2022). A total of 450 paediatric (≤18 years) primary LT recipients were included in the study between January 1998 and December 2019 at two high-volume LT centers in North America. There was a total of 181 rejections accounting for incidence of graft rejection as 40.2% (Barbetta et al. 2022).

Prevalence

Adult Patients

From May 1968 to December 2016, the European Liver Transplant Registry (ELTR) has collected data concerning 146 782 liver transplants in 132 466 patients, from 169 centers, and 32 countries. In recent years about 7300 liver transplants have been performed in Europe annually (Adam et al. 2018). A national cohort study of all adults (66719) who received liver transplant in USA from 1 January 2010 to 31 December 2019 recorded in the OPTN STAR database showed that the number of adult liver transplants per year has steadily increased from 5,731 in 2010 to 8,345 in 2019 (45.6% increase) (Wang et al. 2020).

Paediatric Patients

In 2018, 8250 liver transplants were performed in the USA of which 563 were paediatric liver transplant (PLT) (Kwong and Kim 2020). The number of PLTs peaked at 613 in 2008. ELTR has collected data on LT procedures performed in Europe since 1968. Data extracted from the ELTR for retrospective analysis showed 16,641 PLTs were performed during the study period (May 1968 and December 2017), consisting of 14,515 first PLTs and 2126 re-transplantations. In the last decade, PLTs were performed at a rate of around 650 per year in the ELTR area. Of all PLTs, 25.4% were performed in children aged <1 year at the time of transplant, 37.1% were in children aged 6–12 years, 18.0% were in children aged 6–12 years, and 19.5% in children aged 12 and above (de Ville at al. 2022).

Demographics

Adult Patients

A data analysis from two cohorts; one A2ALL that included 890 LT recipients from 2003 through 2014 and another cohort SRTR that included 45,423 LT recipients from 2005-2013. The mean age in the cohorts was 52.1±11.1 years and 54.2±10.1 respectively with 33% females (Levitsky et al. 2017).

A retrospective analysis of the UNOS de-identified patient-level data of all recipients listed for transplant between 1 March 2002, and 31 December 2012, included 42,508 LT patients. The rates of rejection varied in different age groups ranging from 30.7% for ages 18-25 years to 9.4% for ages 64-69 years (Kueht et al. 2016).

A retrospective case-control study using data from the OPTN conducted from 2000-2011 including 40,593 primary LT recipients reported the age range of 50.3 to 63.6 years with 30.9% female population and 73.4% White ethnicity (Veerappan et al. 2016).

Paediatric Patients

In Europe, a prospective observational study conducted from 2012 to 2016 found that the median age at LT was 2.4 years (0.2-17.9). This study included 55.3% male participants (Goldschmidt et al. 2024). A retrospective cohort study of 2216 PLT recipients between 1 January 2006 to 31 May 2017 using UNOS reported the median age as 2 years (IQR: 0-8) with 49.6% male population (Kanneganti et al. 2022). The median age at transplant was 7.63 months (range, 6.10-11.6 years) with 45% male population in a retrospective study from January 2016 and December 2019 conducted in China (Si et al. 2022).

The Main Existing Treatment Options

The information pertinent to main existing treatment options remains the same as presented in the above section SI.1 Graft Rejection In Allogenic Cardiac Transplant Population.

Risk Factors for the Rejection

Adult Patients

The risk factors for ACR in LT patients include autoimmune etiology of underlying liver disease before liver transplantation (primary biliary sclerosis, primary sclerosing cholangitis and autoimmune hepatitis), cytomegalovirus infection, low levels or noncompliance to immunosuppression, positive lymphocyte cross-match, higher lower recipient age, donor-recipient ethnic origin, male donor into female recipient, higher donor age, higher cold ischemia time and living versus deceased donor liver transplantation (Choudhary et al. 2017).

Paediatric Patients

Cellular rejection is immune-related, with contributing factors including preoperative liver diseases (autoimmune hepatitis, cholestatic liver diseases, HCV), donor/recipient-related factors (ethnic origin, male donor into a female recipient, higher donor age, lower recipient age), surgical-related risk factors (longer cold ischemia time, living vs deceased donor liver transplantation), and postoperative-related factors (CMV/HCV infection, immunosuppression non-compliance/suppressed levels, history of rejection episodes, re-transplantation) (Badwei 2023). Biliary complications (OR: 4.89, 95% CI: 2.00–11.98), donor-negative, recipient-positive Cytomegalovirus mismatch (OR: 9.88, 95% CI: 1.18–82.36), sex mismatch (OR: 3.16, 95% CI: 1.31–8.10), and sex mismatch with a female donor (OR: 3.00, 95% CI: 1.10–7.58) were found to be significant risk factors for acute graft rejection after LT (Dogan et al. 2018). Increased age more than 13 years with relative risk 1.93; 95% CI (1.4–2.7)], primary diagnosis fulminant liver failure, IVIG use in the first week, era of transplant (before 2002 vs. after 2002) and cyclosporin versus tacrolimus-based immunosuppression, were found to be independent risk factors for transplant rejection in paediatric patients (Shepherd et al. 2008).

Natural History of the Indicated Condition in the (Untreated) Population

Adult Patients

The mortality rate by rejection status in A2ALL and SRTR cohorts that 239 graft rejections and 7066 graft rejections respectively was 2.9%; 95% CI (1.4-5.9) and 5.4%; 95% CI (4.9-5.9) respectively (Levitsky et al. 2017).

Paediatric Patients

A retrospective review of 739 ABO-identical/compatible allograft liver biopsies from 199 paediatric transplantation recipients was performed. Out of 7 patients who developed antibody mediated rejection, 2 died accounting for mortality of 1%; 95% CI (0.3-3.6) (Zhou et al. 2021).

Important Co-Morbidities

Adult Patients

A data from the OPTN Standard Transplant Analysis and Research comprising 115,250 adult liver obese and non-obese transplant recipients from 1995 to 2019 in the USA reported history of diabetes (15.40% vs 16.90%), myocardial infarction (0.40% vs 0.70%), alcoholic cirrhosis (11.40% vs 20.80%) in black and non-black population (Yuan et al. 2021).

Paediatric Patients

A data from the Society of PLT registry from 2011 to 2019 comprising 1034 patients were grouped by comorbidities of >1.0% incidence: any supplemental feeding, dialysis,

other abdominal surgery (not Kasai portoenterostomy [KPE]), hepatopulmonary syndrome, and cardiac disease requiring intervention. Patients with biliary atresia with comorbidities have evidence of higher medical acuity at transplant and reduced graft survival; however, they overall did not experience greater incidence of patient death (Taylor et al. 2022).

The morbidity of young adults who underwent liver transplantation as children was high and increased over time. The majority developed complications from immunosuppression or chronic graft dysfunction. More than 1 in 7 patients had a psychiatric disease and 1 in 4 was not perfectly drug adherent (Lund et al. 2023).

SI.3 GRAFT REJECTION IN ALLOGENIC RENAL TRANSPLANT POPULATIONS

Incidence

Adult Patients

A systematic review of 28 studies from 2000 to 2020 reported an incidence of acute antibody-mediated rejection ranging from 1.1% to 21.5% with most studies reporting 3% to 12% incidence, usually within the first-year post-transplant (Hart et al. 2021).

A comparative population-cohort analysis between 2003 and 2013 studying cancer-related outcomes in kidney allograft recipients included 18,493 and 11,602 adult recipients from England and New York state (NYS) respectively. For kidney allograft recipients with post-transplant cancer, the incidence of kidney transplant rejection/failure was found to be 26.9% and 69.0% for England versus NYS respectively. For kidney allograft recipients without post-transplant cancer, the risk for kidney transplant rejection/failure was 25.4% versus 50.8% in England versus NYS respectively (Jackson-Spence et al. 2017).

A retrospective, cohort study using data from Hospital Episode Statistics (HES) of 12,902 kidney-alone transplant procedure performed in England between January 2003 and December 2014 estimated the difference in outcomes for weekend hospital admissions. The incidence of 1-year kidney allograft failure/rejection was found to be 16.7% and 16.8% in weekend and weekdays transplantations respectively (Anderson et al. 2017).

Data on patients receiving kidney transplantation were obtained retrospectively from a cohort that consisted of patients from 2 tertiary referral centers in Korea from 2000-2011 and included 1786 patients. During the follow-up period, 163 (9.1%) had at least one episode of acute rejection in the 3 months after the kidney transplantation (Han et al. 2016).

Paediatric Patients

The multicenter comparative analysis included the CRADLE trial and the Cooperative European Paediatric Renal Transplant Initiative registry (CERTAIN registry). The study encompassed a total of 54 KT patients in the CRADLE trial and 554 KT patients in the CERTAIN registry. The incidence of acute rejection in KT patients was 5.6% in the CRADLE trial study and 7.8% in the CERTAIN registry, occurring at one-year post-transplant (Patry et al. 2023). A total of 4069 kidney-only transplant paediatric patients were included from 2002-2017 in a North American Paediatric Renal Trials and Collaborative Studies special study (NAPRTCS) database. A total of 507 paediatric patients developed acute rejection prior to 12 months post-transplant accounting for incidence of 12.4%; 95% CI (11.5-13.5) (Barton et al. 2021). A retrospective cohort analysis using the UNOS database identified 13947 paediatric recipients of kidney transplant between 2000 and 2018 in the US. The graft failure was reported in 3666, accounting for an incidence of 26.3% (Patel et al. 2021). Data from the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry included 628 children aged 2-18 years of age who had received their first kidney transplant between 1 January 1994 and 31 December 2013. A total of 102 (16.2%; 95% CI 13.3-19.1%) experienced their first acute rejection within the first 6 months after transplantation (Ladhani et al. 2017).

Prevalence

Adult Patients

Based on the 2021 data of the ERA registry, in the participating countries 12 244 kidney transplantations were performed in 2021, corresponding to a kidney transplantation rate of 41.6 per million population. Based on the 2021 data from the USDRS, 17 357 kidney transplantations were performed in the USA, corresponding to a kidney transplantation rate of 77.0 per million population (Stel et al. 2024).

Paediatric Patients

The overall number of kidney transplants performed annually was stable and varied between from 3.1 to 3.9 per million age-related population (APC: − 1.4%, 95% CI: − 2.8-0.1) in patients aged 0–14 years between 2007 and 2016 (Bonthuis 2021).

Demographics

Adult Patients

A retrospective cohort study from Korea included 1786 patients with a mean age of 42.9±11.17 years and 61% male population (Han et al. 2016).

In a retrospective, cohort study using data from HES of 12,902 kidney-alone transplant procedure performed in England between January 2003 and December 2014, the patient cohort demographics were mean age 49.9±13.4 years, 62.5% males, with White ethnicity 74.7% (Anderson et al. 2017).

A comparative population-cohort analysis between 2003 and 2013 studying cancer-related outcomes in kidney allograft recipients included 18,493 and 11,602 adult recipients from England and NYS respectively with a mean age of the population 47.61 years and 50.9 years with 61.5% and 60.6% males in England and NYS respectively (Jackson-Spence et al. 2017).

Paediatric Patients

According to the NAPRTCS transplant registry and using data from PHIS (2010-2019), the mean age of paediatric KT recipients was 12.0±5.16 years with 57.3% male. Among this KT population, 24% were aged 0 to 4 years, 17.7% were aged 5 to 9 years, 23.7% were aged 10 to 14 years, 23.3% were aged 15 to 17 years, and 11.3% were aged 18 years and above (Erez et al. 2023). A retrospective cohort analysis identified 13947 paediatric recipients of kidney transplant between 2000 and 2018. Median age of recipients was 12 [IQR: 7-15] years, 59.1% were male and 51.5% were white (Patel et al. 2021). A study included 884 paediatric (age: 0-17 years old) kidney transplant recipients at the University of Minnesota from 1963 to 2015. The mean age of the cohort was 9.1 ± 5.6 years with recipients more likely to be male (59%) and White (89%) (Serrano et al. 2018).

The Main Existing Treatment Options

The information pertinent to main existing treatment options remains the same as presented in the above section SI.1 Graft Rejection In Allogenic Cardiac Transplant Population.

Risk Factors for the Rejection

Adult Patients

Highly sensitized kidney transplant recipients with peak panel reactive antibody greater than 80% were found to have a greater risk of rejection, and graft failure (Lim et al. 2015). Different factors such as younger recipient age, old donor age, African American race, HLA mismatching, presence of donor specific antibody as some important risk factors for acute rejection risk following kidney transplantation (Lebranchu et al. 2014).

Paediatric Patients

The risk factors for acute rejection after KT included mismatches [sub-distribution hazard ratio (SHR): 1.36, 95% CI (1.1-1.6)], immunosuppression with cyclosporine, prednisone, and azathioprine [SHR: 2.2, 95% CI (1.1-4.3)], delayed graft function [HR: 2.49, 95% CI (1.57-3.93)], cytomegalovirus infection [HR: 5.52, 95% CI (2.27-11.0)], and poor adherence [HR: 2.28, 95% CI (1.70-4.66)] (do Nascimento Ghizoni Pereira et al. 2021). A study using the data from the ANZDATA Registry (1994-2013) estimated that children with obesity were more likely to experience renal graft loss than those with normal weight with adjusted hazard ratios [HR: 1.61 95% CI (1.05-2.47) (Ladhani et al. 2017). Other risk factors associated with rejection in paediatric kidney transplant patients were

cold ischemia time [HR:1.38; 95% CI (1.25–1.60)], acute rejection [HR: 1.68; 95% CI (1.55–3.84)], re-transplant [HR: 2.7, 95% CI (1.76–3.98) and deceased donor type [HR: 2.96; 95% CI (1.75-4.69)] as independent risk factors for graft loss at 10 years post-transplant (Aoki et al. 2020).

Natural History of the Indicated Condition in the (Untreated) Population

Adult Patients

A retrospective population-based cohort study using linked healthcare databases within the Alberta Kidney Disease Network included 520 kidney transplant recipients between 1 May 2002, and 31 December 2015, in Alberta, Canada reported 206 deaths in the kidney transplant recipient group accounting for mortality rate of 40%; 95% CI (35.5-43.9) (Lam et al. 2020).

Paediatric Patients

Data from the ESPN/ERA-EDTA registry from 4459 patients aged 0-14 years from 22 European countries who initiated kidney replacement therapy between 2007 and 2016 showed an overall 1-, 2-, and 5-year patient survival of 97.6%, 96.4% and 94.4%, respectively. The total number of patients who died was 225 (5%) after a median follow-up of 4.1 years. Cause of death was reported as cardiovascular disease (28.9%), followed by infections (22.7%), and for 23.1% of patients, the cause of death was missing or unknown (Bonthuis 2021).

Retrospective data from the Australian and New Zealand Dialysis and Transplant Registry on 1810 kidney transplant patients under 20 years, who received their first kidney transplant from 1970 to 2015 showed 431 (24%) patient deaths, 183 (42%) of which occurred with transplant function and 248 (58%) of which occurred on dialysis after transplant failure. The authors reported a total of 28 deaths (10%) among those transplanted 1998-2004 and 9 deaths (2%) among those transplanted in 2005–2015 (Francis et al. 2020).

Adverse pregnancy outcomes

The female recipient of heart, liver and kidney transplant has been consistently associated with increased risks of adverse pregnancy outcomes compared with the general population such as preterm births, stillbirths, cesarean deliveries, pre-eclampsia, and miscarriages.

Important Co-Morbidities

Adult Patients

A retrospective population-based cohort study using linked healthcare databases within the Alberta Kidney Disease Network included 520 kidney transplant recipients between 1 May 2002, and 31 December 2015, in Alberta, Canada. The common co-morbidities

present in the kidney transplant recipients were hypertension (66%), diabetes (37%), chronic pulmonary disease (13%), heart failure (12%), and peripheral vascular disease (8%) (Lam et al. 2020). Another study on patients receiving kidney transplantation, obtained retrospectively from a cohort that consisted of patients from 2 tertiary referral centers in Korea from 2000-2011 included 2885 patients. The common co-morbidities present were hypertension (86.3%), diabetes (20.2%), and liver cirrhosis (1.1%) (Han et al. 2016).

Paediatric Patients

A study included 79 children with proliferative Lupus Nephritis (LN) from a LN registry of the German Society of Paediatric Nephrology between 1997 and 2015. A 12-month renal outcomes and comorbidities were assessed in these predominantly Caucasian children treated with cyclophosphamide and mycophenolate mofetil (MMF). During presentation, the 46 children (58.2%) had acute renal failure, 39 patients (49.4%) had nephrotic range proteinuria and 64 children (81%) had hypertension. Other major treatment-associated comorbidity within the first year of treatment were: infections (23%), upper gastrointestinal symptoms (17.7%), menstrual disorders (20%), cushingoid syndrome (30.4%) and striae distensae (16.4%) (Suhlrie et al. 2020).

PART II: MODULE SII— NONCLINICAL PART OF THE SAFETY SPECIFICATION

The hematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day for renal transplant recipients. Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended doses. Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure). The nonclinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events (AEs) observed in human clinical trials which now provide safety data of more relevance to the patient population (Syntex Report No. AT 6742 1994).

SII.1.1 Carcinogenicity

In experimental models, mycophenolate mofetil was not tumorigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2 – 3 times the systemic exposure (area under the curve (AUC) or C_{max}) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3 – 2 times the systemic exposure (AUC or C_{max}) observed in cardiac transplant patients at the recommended clinical dose of 3 g/day (Chellman and Pulley 1994a, Chellmann and Pulley 1994b).

SII.1.2 Genotoxicity

Two genotoxicity assays (the mouse lymphoma/thymidine kinase assay and the mouse micronucleus aberration assay) indicated a potential of mycophenolate mofetil to cause chromosomal instability at severely cytotoxic dose levels. Other genotoxicity tests (the bacterial mutation assay, the yeast mitotic gene conversion assay or the Chinese hamster ovary cell chromosomal aberration assay) did not demonstrate mutagenic activity (Kirchner 2000, Chetelat 2000, Jagannath et al. 1987a, Jagannath et al. 1987b, Murli et al. 1987, Blachman 1989, Ivett 1988).

SII.1.3 Impairment of Fertility

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. The systemic exposure at this dose represents 2 to 3 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and 1.3 – 2 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first-generation offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation (Chellman and Altera 1989a, Chellman 1994b).

SII.1.4 Reproductive Toxicity:

In teratology studies in rats and rabbits, fetal resorptions and malformations occurred in rats at 6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. The systemic exposure at these levels was approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients (Chellman and Altera 1988, Chellman and Altera 1989c).

Non-clinical evidence shows that the dose of mycophenolate that could be transferred via the seminal fluid to a potentially pregnant partner is 30-fold lower than the concentration without teratogenic effects in animals, and 200-fold lower than the lowest teratogenic concentration in animals. Therefore, the risk of harm mediated via seminal fluid is considered negligible.

PART II: MODULE SIII— CLINICAL TRIAL EXPOSURE

Since the product has been marketed for 29 years, it is not feasible to obtain a precise cumulative list of Company-sponsored interventional studies. Therefore, this section includes exposure from interventional clinical trials entered in the Company databases conducted with MMF as an investigational drug since International Birth Date (IBD) until PBRER DLP (2 May 2025).

The cumulative exposure to MMF was obtained from Clinical Study Reports, the clinical study database, the Investigator Brochure, and the Integrated Safety Summary. Exposure was based on actual treatment for unblinded studies. For crossover and dose-escalation studies, the number of patients who received a given treatment in any included study period was counted; if some patients were assigned to more than one treatment, the exposure numbers may total more than the study enrollment number for this reason.

The available cumulative exposure to MMF, placebo, and other investigational medicinal products in Company-sponsored interventional clinical trials where MMF was used as an investigational drug is presented in Table 2.

Table 2 Cumulative Patient Exposure to mycophenolate mofetil in Clinical Trials with Product as an Investigational Drug

Trial Status	Mycophenolate mofetil	Other IMPs	Placebo
Completed prior to PBRER (DLP 2 May 2025)	16,226	6339	778

IMP = Investigational Medicinal Product.

The cumulative clinical trial exposure data are presented for MMF by demographic characteristics are presented in below table.

Table 3 Cumulative Exposure to Mycophenolate Mofetil in Company-Sponsored Interventional Trials by Patient Demographic Characteristics

Demographic Characteristic	Mycophenolate mofetil
Age (years)	
<18	451
⩽18 and ⩾65	10,906
>65	564
Unknown	4305
N	**16,226**
Sex	
Female	6116
Male	9852
Unknown	258
N	**16,226**
Race/Ethnicity	
American Indian or Alaska Native	29
Asian	939
Black/African American	932
Multiple	3
Native Hawaiian or Other Pacific Islander	17
Other	625
White	7870
Unknown	5811
N	**16,226**

Since the IBD (3 May 1995), an estimated total of 73 paediatric patients have received MMF via participation in Company-sponsored clinical trials conducted in the paediatric patient group (paediatric studies NO15318, PA16497, and PA16215). Since the IBD (3 May 1995), an estimated total of 451 paediatric patients have received MMF in all Company-sponsored clinical trials for which the data are available.

PART II: MODULE SIV— POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Cellcept has been marketed for over 28 years and what is known about the safety profile of this product is now primarily based on post marketing experience.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Not applicable.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Use in Pregnancy and Lactation

Measurement of the passage of MPA into breast milk in a patient with LN (Huerta et al. 2021).

Mycophenolic acid (MPA) is contraindicated in women who are breastfeeding, based on animal data. It is unknown whether MPA is excreted in human breast milk. A female patient with class IV LN reinitiated MPA treatment in substitution of azathioprine (AZA) used during pregnancy, due to a LN reactivation in peripartum. Serial breast milk and blood samples were collected (pre-dose; 2- and 4-hours post-dose) to measure MPA concentrations at steady-state. MPA levels were measured with high performance liquid chromatography. Authors found that MPA transferred markedly from her blood stream to her human milk, with MPA milk concentrations of 35 mg/L (pre-dose), 80 mg/L (2 hours post-dose), and 28 mg/L (4 hours post-dose). Usually, a relative infant dose of 5%–10% is used as a reference cut-off point for the breastfeeding drug exposure risk assessment. This study case provides new information about a knowledge gap. Data from this case indicates that relatively high amounts of MPA are excreted into breast milk, with peak milk levels at about 2 hours after a dose of the delayed-release formulation of MPA.

The final decision on breastfeeding continuation should consider additional factors—the type of drug, its metabolism and safety profile, the risk of higher drug exposures in neonates, owing to immature drug-elimination capacity, and the actual benefits of breastfeeding. In this case study the patient was advised against continuing breastfeeding, as the infant's daily intake could be within the therapeutic range, leading to not only potential gastrointestinal side effects and increased risk of infections but also deleterious effects on the maturation of the immune system (Krutsch et al. 2023).

While studies in rats have shown MMF to be excreted in milk, the relevance of this finding to humans is unknown. Following oral and IV administration in humans, MMF undergoes rapid and extensive absorption and complete pre-systemic metabolism to the active metabolite, MPA. It seems therefore unlikely that MMF as such can be found in plasma and milk. The Marketing Authorization Holder (MAH) cannot comment whether the delayed-release formulation of MPA used in this study case would make a difference with regard to the relevance of the finding for MMF. There is very limited experience about the safety of the exposure of infants to MPA through breastfeeding. The National Transplantation Pregnancy Registry/ Transplant Pregnancy Registry International collected information on 6 mothers who received kidney or heart transplants and who

breastfed 7 infants while taking a mycophenolate product. The maximum time that any of the infants was breastfed was 14 months. None of the infants had any reported adverse reactions due to breast-feeding (Constantinescu et al. 2014). An Australian case series reported 3 women with heart transplants who had a total of 5 infants, all of whom were breastfed (extent not stated). Two of the women took mycophenolate mofetil postpartum, one in a dosage of 720 mg twice daily and the other woman in a dosage of 1 g twice daily. No adverse infant effects were reported up to the times of hospital discharge (Boyle et al. 2021). Due to very limited data, as discussed above, and the potential for serious adverse reactions in nursing infants, CellCept is contraindicated during breastfeeding (CDS, section 2.3 Contraindication).

USA Risk Evaluation and Mitigation Strategy (REMS) - Pregnancy Registry

A USA based Mycophenolate Pregnancy Registry (Study ML22679) was ongoing as part of the U.S. shared system REMS for MMF during the reporting interval. The goal of the mycophenolate REMS is to mitigate the risk of embryo fetal toxicity associated with use of MMF during pregnancy by educating healthcare providers (HCPs) on the following:

- The increased risks of first trimester pregnancy loss and congenital malformations associated with exposure to MMF during pregnancy.
- The need to counsel females of reproductive potential on the importance of pregnancy prevention and planning when taking mycophenolate.
- The need to report pregnancies to the Mycophenolate Pregnancy Registry
- Informing female patients of reproductive potential who are prescribed MMF about:
  - The increased risks of first trimester pregnancy loss and congenital malformations when taking mycophenolate during pregnancy.
  - The importance of pregnancy prevention and planning when taking mycophenolate.

In a Major REMS Modification Notification letter to Sponsors on 2 August 2019, the Food and Drug Administration (FDA) indicated that, based on the data included in previous REMS assessment reports, the REMS was not meeting its goals. Therefore, the FDA determined that the previous approved REMS for mycophenolate was to be modified to ensure that the benefits of the drug outweigh its risks. The modified REMS was approved on 15 January 2021 and the reporting interval for assessment reports was changed from 12 months to 18 months.

The Year 10 report of the mycophenolate REMS covered the period from 16 May 2022 through 15 November 2023 (second 18-month report) and the highlights of the report are presented below.

During the reporting period, all functional aspects of the mycophenolate REMS have operated successfully. No concerns were reported. A total of 14,083 prescribers have

confirmed training in the Mycophenolate REMS since launch of the REMS. Of these, 289 prescribers confirmed training during the reporting period through either the *Mycophenolate REMS Prescriber Training Confirmation Form* or the *Mycophenolate REMS Center Training Confirmation Form*. Transplantation, Nephrology, Pediatrics and Rheumatology, cs were the most frequently reported specialties, totaling 58.7% of these training confirmations.

- During the reporting period, a total of 24,393 prescribers complete REMS-compliant continuing education (CE) activities.
- Based on monthly prescription data, there were 92,524 HCPs actively prescribing mycophenolate-containing products during the reporting period. Of these active prescribers, 7,190 (7.8%) have confirmed training in the Mycophenolate REMS since the launch of the program. Mycophenolate was most prescribed by specialists in Internal Medicine, Nephrology, Neurology, Dermatology, and Rheumatology. The majority of these prescribers are non-transplant specialists.

The Mycophenolate Pregnancy Registry reported 20 new eligible pregnancies during the reporting period, for a total of 243 since launch of the REMS.

- Eleven of the 20 pregnancies from the reporting period were missing data on the intent to become pregnant or had an unknown intent; 8 pregnancies were reported as not intended and one pregnancy was reported as intended. Twelve of the cumulative pregnancies were reported as intended.
- Pregnancy outcomes are known for 13 of the 20 pregnancies in this reporting period (4 induced abortions, 7 spontaneous losses, and 2 live births).
- Pregnancy outcomes are known for 157 pregnancies since the beginning of the REMS (14 induced abortions, 64 spontaneous losses, 2 fetal deaths, 1 ectopic pregnancy, and 76 live births).
- Thirty congenital anomalies in 13 pregnancy cases have been reported since the launch of the REMS; there were no new congenital anomalies reported during the reporting period. Of these 13 pregnancy cases, there were 10 live births, 2 spontaneous abortions/miscarriages, and 1 unknown outcome. Thirteen of the congenital anomalies were classified as major malformations, 3 were classified as other conditional anomalies, 2 were chromosomal anomalies/genetic disorders, 2 were prematurity related malformations, and 10 could not be determined.

PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

The patient exposure to CellCept® (mycophenolate mofetil, MMF) based on marketing experience or commercial data is calculated according to the following methodology and assumptions:

- The estimation of patient exposure is based on the volume of product sold in the following regions: European Economic Area (EEA), United States (US), ASIA, and Rest of World (RoW).
- In the ASIA region CellCept® is approved for both Transplant Rejection Prophylaxis and Lupus Nephritis (LN), and the estimated exposure for this region is provided for each indication (Transplant and LN). The countries included in the ASIA region are: China, India, Taiwan, Thailand, Bangladesh, Indonesia, Philippines, Myanmar and Nepal, which are the countries where the LN indication is currently approved.
- The new specifications for the ASIA region include data that were compiled from information directly obtained from affiliates in 4 countries of this geographic area (China, India, Taiwan and Thailand), which were taken as a reference for the estimation of patient exposure in the ASIA region.
- For the US, EEA, and RoW, transplant patient exposure was determined from an epidemiological forecast model based on registry data. The model takes into account both patient survival and patient compliance. The estimated Average Annual Dose for transplant indication in the US, EEA and RoW are based on Real World Patient Data from:
  - IMS Disease Analyzer for EEA and RoW (sample size: 450 patients);
  - Truven for the US (sample size: 3,823 patients).

The estimation of the market exposure to CellCept® was estimated based on the volume of mycophenolate mofetil sold. The volume sold by Roche is sourced from Roche supply chain and financial systems (Controlling Profitability Analysis [COPA]). The sales data are provided on a monthly basis; therefore, the exposure is available from the IBD to the nearest point of DLP (i.e., 30 April 2025). The data from Zahravi Pharmaceuticals is not included in this reporting interval (data directly taken from SAP data)

The patient exposure to CellCept® is expressed in patient year and is estimated based on the Volume of product sold and the average yearly dose per patient in each one of the geographical regions mentioned (US, EEA, RoW). The ASIA region has been removed from the final table and all the countries within this region have been added to RoW. The calculation for patient year is the following:

Patient year = Total Volume of CellCept® sold / Total annual dose per patient; which is valid for both indications (Transplant Rejection Prophylaxis and LN).

The estimated Average Annual Dose of CellCept® treatment in the US is 503.6 g and 502.5 g in both, EEA and RoW (Table 4).

Table 4 Estimated Annual dose per region

Country/Region	Estimated Annual Dose (g)
US	503.6

Table 4 Estimated Annual dose per region (Cont.)

EEA	502.5
RoW	502.5

The estimated Average Annual Dose per patient in the ASIA region is 447.2 g for Transplant Rejection Prophylaxis and 503.6 g for Lupus Nephritis. The treatment split by indication is 11.7% for Lupus Nephritis and 88.3% for Transplant (Table 5). This means that of the total volume of CellCept® sold in the ASIA region, 11.7% is used in Lupus Nephritis patients and 88.3% is used in transplant patients.

Table 5 ASIA Region Estimated Annual Dose and patient split by indication

ASIA Region	**Indication**	
	Lupus Nephritis	**Transplant**
Estimated Annual Dose (g)	503.6	447.2
Treatment Split (%)	11.7	88.3

Methodology: Japan

Chugai Data Methodology:

The patient exposure is determined from the following method.

(Facts based on the marketing data)

- Number of capsules sold in reporting period: 154,894,900
- Number of bottles solid in reporting period: 571,844

(Facts based on the MDV (Medical Data Vision) data)

Indication	**Sex**		**Age (years)**				
	M	**F**	**≤16**	**>16 to 65**	**>65**	**Average dosage (capsules/day)**	**Average administration period(day)**
Organ transplants	62.50%	37.50%	1.70%	75.80%	22.50%	3.9	305.8
Lupus nephritis	24.10%	75.90%	5.50%	71.80%	22.70%	5.2	283.6
SSc-ILD	7.70%	92.30%	2.00%	56.00%	42.00%	-	-

M: = Male; F: = Female

Calculation formula for each indication

- The patient exposure of reporting period = Number of capsules sold in reporting period × Disease Ratio(%) ÷ [Average dosage (capsules/day) × Average administration period (days)].

Calculation formula for Oral Suspension (OS)

- OS is used only for organ transplant patients (assumption from marketing experience)
- The patient exposure of reporting period = Number of bottles sold in reporting period ÷ Number of bottles per patient in reporting period (bottle/patient/year) *.
- *Number of bottles per patient in reporting period (bottle/patient/year) = 6(bottle).

SV.1.2 Exposure

Since the IBD (3 May 1995) up to 2 May 2024, a cumulative exposure of 9.75 million patient-year has been estimated based on commercial data for MMF.

Table 6 Cumulative Exposure from Marketing Experience

Duration	Estimated patients exposed (patient years)
3 May 1995 to 2 May 2025	10.23 million patient years

PART II: MODULE SVI— ADDITIONAL E.U. 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

Not applicable.

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 marketing authorisation application for MMF was approved in 1995. No RMP was included in the initial submission. A summary of the safety concerns for MMF that were not considered for inclusion in the list of Safety Concerns in the RMP because they are not associated with additional pharmacovigilance (PV) activities or RMM is included here for completeness.

Table 7 Safety Concerns that are not associated with additional PV activities or RMM

Risk	Safety Concern (EU SmPC)	Additional PV/RMM
Important Identified Risks	• Bone Marrow Depression Resulting in Cytopenias and Associated Infections or Hemorrhages • Gastrointestinal disorders including ulceration and hemorrhage • Hypersensitivity • Drug-drug interaction (DDI) – Drugs that interfere with the enterohepatic circulation and may lead to reduced efficacy of mycophenolate mofetil • Lymphomas and other malignancies, particularly of the skin	None
Important Potential Risks	• Exacerbation of hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) • DDI – Risk of activation of live vaccines • DDI – Lack of effect of any vaccinations • DDI – Potential interaction with AZA leading to increased bone marrow suppression	None
Missing Information	• None	None

AZA = azathioprine; DDI = drug-drug interaction; EU SmPC = European Union Summary of Product Characteristics; HGPRT = hypoxanthine-guanine phosphoribosyl-transferase; PV = pharmacovigilance; RMM = risk minimisation measure.

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

Important Identified Risk: Adverse Pregnancy Outcomes including Teratogenicity and Mutagenicity

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Following endorsement from PRAC for Cellcept- PBRER 1139314, PSUSA/00010550/202505 dated 15 January 2026 the following missing information has been removed from the EU RMP

Long term safety (growth retardation, pubertal maturation and fertility, bone health, metabolic problems and neurocognitive development)" is no longer presented in the EU RMP as a missing information

Reasons for changes/ removal to the list of missing information:

Based on the annual Drug Safety Report submitted to further characterise the missing information during the PBRER reporting interval (1139314), the PRAC agreed with the MAH's conclusion that the cumulative PSUR review does not indicate a high occurrence of paediatric long-term ADRs and that further data generation is expected to be limited. The PRAC considers that Roche may include the review of this risk within routine PSUR submissions, and that submission of separate annual reports in addition to the PSUR review is not warranted.

As monitoring can be adequately managed through routine PSUR assessments without additional pharmacovigilance or risk minimisation measures, the missing information no longer meets the criteria for important missing information and its removal from the RMP is justified.

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

SVII.3.1.1 Information on Important Identified Risk: Adverse Pregnancy Outcomes including Teratogenicity and Mutagenicity

<table>
<tr>
<td>Background incidence/ prevalence</td>
<td>
Transplant patients: Post-transplantation pregnancies should be monitored as high-risk and they require close maternal and fetal surveillance through coordinated care among maternal-fetal medicine specialists and transplant personnel. Based on publications, the reported risk for spontaneous abortions in female organ transplant recipients receiving immunosuppressants other than MMF varied between 12% and 33%, according to the type of immunosuppressant and type of transplanted organ. The risk for malformations is about 2% per live births in the overall European population and is 4-5% for female organ transplant recipients in the United States (US) receiving immunosuppressants other than MMF.
General population
Epidemiologic information on pregnancy and its outcomes provided in this subsection comes from the U.S. and are summarized in the table below (DSR 1059599):
<table>
<tr><td></td><td>2004</td><td>2008</td><td>2012</td></tr>
</table>
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</tr>
</table>

Incidence of pregnancy in women in the reproductive age group (number of pregnancies in millions)	103 per 1000 women (6.4 M) (Ventura 2008, Joseph KS 2007)	105.5 per 1000 women (6.5 M) (Ventura SJ 2012)	63.0 per 1000 women (Martin JA 2013)
Pregnancy outcome Live births Abortions Foetal losses	4.1 M (64%) 1.22 M (19%) 1.06 M (17%) (Ventura SJ 2008)	4.24 M (64.5%) 1.21 (18.5%) 1.12 M (17%) (Martin JA 2013)	Not available

About 1 of 33 newborns present birth defects in the USA (Centers for Disease Control and Prevention. Birth Defects 2023) and about 1 in 40 newborns (125,000 in 5,000,000) have a congenital anomaly in the European Union. Congenital anomalies are a leading cause of fetal death, infant mortality and morbidity in childhood worldwide (Kinsner-Ovaskainen A 2021).

Transplant population:

Female transplant recipients in general are at higher risks for certain pregnancy outcome complications than the general female population. There is an increased risk of first trimester spontaneous abortions, preterm delivery, low birth weight and intra-uterine growth retardation.

The incidence of live births ranges from 59% to 90%, spontaneous abortions from 6% to 21%, induced abortions from 4% to 29%, stillbirths from 0% to 9%, and low birth weight (<2500 g) from 9% to 80% of live births (Coscia LA 2008). The incidence of pre-term delivery is high and ranges from 10% to 78% of live births.

Female patients with liver or heart transplants are less likely to have premature births than kidney transplant recipients and the mean birth weight and maturity of their infants are greater (Coscia LA 2008).

Lupus patients: In patients with SLE, both LN and anti-phospholipid antibodies increase the risks for maternal hypertension and premature births. A systematic review of 37 studies, which included 2,751 pregnancies in 1,842 women with LN, reported maternal complications including lupus flare (25.6%), hypertension (16.3%), nephritis (16.1%), pre-eclampsia (7.6%), and eclampsia (0.8%). The induced abortion rate was 5.9% and when excluded, foetal complications included spontaneous abortion (16.0%), stillbirth (3.6%), neonatal deaths (2.5%), and intrauterine growth retardation (12.7%). The unsuccessful pregnancy rate was 23.4% and premature birth rate was 39.4% [Smyth et al, 2010].

Frequency

Regardless of the indication for MMF treatment, categorization (i.e. retrospective or prospective), or geography (US or Europe), the risk for malformations in MMF exposed pregnant women was reported to be between 23% and 27% per live births (Hoeltzenbein et al. 2012).

For spontaneous abortions, based on publications, the reported risk for MMF-exposed pregnant women was between 45% and 49% (in Hoeltzenbein et al.: 45% with a 95% CI based on survival techniques of 29 to 66%)

Published studies are summarized in the table below:

	(Hoeltzenbein et al. 2012)	(Jones et al. 2013)

	Patients	57 women treated with MMF. Treatment indication: Organ transplant (22) SLE (23) Other autoimmune disease (12)	205 pregnancies fathered by 152 males treated with MMF. Treatment indication: Organ transplant
	Spontaneous Abortion	16 (28.07%)	14
	Elective termination	12 (21.05%)	-
	Live births	29 (including 6 with major defect)	194 (including 21 premature births)
	Comments	The results confirm a high incidence of major malformations (26%) after exposure to MPA in first trimester. It was stated that, apart from exposure to MPA, the underlying maternal disease and concomitant medications might also have contributed to adverse pregnancy outcomes such as a high rate of spontaneous abortions, prematurity (62%), and low birth weight (31%).	It was concluded that the outcomes of pregnancies fathered by transplant recipients treated with MPA products appeared similar to outcomes in the general population.
Risk groups or risk factors	Pregnant women or women of child-bearing potential.		
Potential mechanisms	No specific mechanism of teratogenicity and mutagenicity has been identified. However, preclinical tests show that foetal resorptions and malformations occurred in rats at 6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. No effect was seen on the fertility of male rats treated with MMF (Chellman G and Altera K 1989a, Chellman G and Altera K 1990). Two genotoxicity assays (the mouse lymphoma/thymidine kinase assay and the mouse micronucleus aberration assay) indicated a potential of MMF to cause chromosomal instability at severely cytotoxic dose levels.		
Preventability	Female patients CellCept is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods. Before the start of treatment, female patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention and planning. Prior to starting therapy with CellCept, female patients of childbearing potential must have a negative serum or urine pregnancy test with a sensitivity of at least		

	25 mIU/mL; a second test should be performed 8-10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur. Women of childbearing potential should use two reliable forms of contraception simultaneously, at least one of which must be highly effective, before beginning CellCept therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception. Male patients In the absence of sufficient data to exclude a risk of harm to the fetus conceived during or directly after the treatment of the father, the following precautionary measure is recommended: sexually active male patients and/or their female partners are recommended to use effective contraception during treatment of the male patient and for at least 90 days after cessation of treatment (DSR 1078058). All patients Due to the theoretical risk of adverse pregnancy outcomes if the blood of a patient treated with drugs with known teratogenic potential is transfused to a pregnant female, patients should not donate blood during therapy and for at least 6 weeks following discontinuation of CellCept (DSR 1073518). Men should not donate semen during therapy or for 90 days following discontinuation of CellCept. Instructions for handling CellCept tablets and capsules should not be crushed or opened. Patients should also avoid inhalation or contact of the skin or mucous membranes with the powder contained in CellCept capsules and oral suspension (before reconstitution). Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the bottle/cap and the table after reconstitution (Air monitoring results of drug product exposure during reconstitution of powder for oral solution).
Impact on individual patient	Given the nature of the AE, the impact on the patient's quality of life is high.
Potential public health impact of safety concern	None. The total number of pregnancies exposed to CellCept remains low.

AE = Adverse Event; CI = Confidence Interval; DSR = Drug Safety Report; LN = Lupus Nephritis; MMF = Mycophenolate mofetil; MPA = Mycophenolic acid; SLE = Systemic Lupus Erythematosus; US = United States.

SVII.3.1.2 Information on Important Potential Risks

None.

SVII.3.2. Presentation of the Missing Information

None

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 8 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Adverse pregnancy outcomes including Teratogenicity and Mutagenicity
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

ROUTINE PHARMACOVIGILANCE ACTIVITIES BEYOND ADVERSE REACTIONS REPORTING AND SIGNAL DETECTION

The MAH proactively identifies and evaluates potential safety issues from reported AEs and other available safety data and assesses the potential impact of this data on the risk profile of Company products. Established routine pharmacovigilance and signal generation activities are used to capture and review safety information, including cases entered onto the Company Global Safety Database and information retrieved for other sources including from Regulatory Authorities.

Signal generation strategies are employed to systematically review safety data:

- **Periodic Review of Safety data**: Serious Unexpected Related cases; death cases; pregnancy and lactation cases; off-label use cases; lack of efficacy cases; cases of AEs in children < 18 years old; cases of medication errors; cases involving elderly patients; cases in patients with renal, hepatic or cardiac impairment; cases involving drug interactions; and incomplete cases.
- **Literature**: Systematic, regular searches of internationally recognized biomedical databases are reviewed for publications reporting potential signals.
- **Disproportionality analysis**: The MAH/ Marketing Authorization Application (MAA) conducts a quantitative review of data in the Company Global Safety Database and analyze potential signals using disproportionality analysis.
- **Trending Analysis for Potential Product Defects**: On a quarterly basis, trends in certain categories of AE reports (e.g., death, lack/loss of effect) are statistically monitored to identify potential product defects which may appear through AE reports. For all identified safety concerns routine pharmacovigilance activities are performed, with the objective of continuously monitoring the safety profile of the drug, including updates of labeling if needed.

The Roche standard pregnancy follow-up process was implemented for all products to request additional information on the medication history of the exposed parent, relevant

medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life..

Cumulative data will be presented in Periodic Safety Update Reports (PSURs)/PBRERs.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no ongoing or planned post authorization efficacy studies for this product.

PART V: RISK-MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK-MINIMIZATION ACTIVITIES)

RISK-MINIMIZATION PLAN
V.1 ROUTINE RISK-MINIMIZATION MEASURES

Upon compiling the important risk(s), the MAH determines the appropriate risk minimization activities that are needed to address the listed risk(s). This assessment is based on but not limited to the unique nature of the important risk(s) themselves but also on the various factors that impact the end-user (e.g., patient, health care providers, etc.) who are targeted by the appropriate risk minimization activity.

Routine risk minimization activities are a collection of activities that are applicable to all medicinal products. Examples of routine risk minimization activities include the following:

- Summary of Product Characteristics
- Labeling
- Package leaflet
- Pack size
- Legal status of the medicinal product

Should the nature of the important identified and important potential risk(s)be of such nature that routine risk minimization activities are not sufficient, the MAH develops additional risk minimization activities tailored to the specific needs of the targeted end-user(s) with respect to the nature of the specific important risk(s).

Table 9 Description of Routine Risk-Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization
Adverse Pregnancy Outcomes including Teratogenicity and Mutagenicity	**Routine risk communication:** Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Legal status:** CellCept is a prescription only medicine

EU SmPC = European Union Summary of Product Characteristics.

V.2. ADDITIONAL RISK-MINIMIZATION MEASURES

Table 10 Safety Concern: Pregnancy Adverse Effects including Teratogenicity and Mutagenicity

Additional risk-minimization measure	**Educational Guide for Healthcare Professionals**
Objective(s)	The educational materials are intended to inform and assist healthcare professionals (HCPs) in communicating key safety messages to patients or their parents receiving mycophenolate mofetil, and to provide patients with important safety information. The objective is to minimize the number of pregnancies exposed to MMF.
Rationale for the additional risk-minimization activity	Mycophenolate is a powerful human teratogen. Spontaneous abortion and congenital malformations have been reported following mycophenolate exposure during pregnancy. Therefore, CellCept is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Physicians should ensure that women taking mycophenolate understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.
Target audience and planned distribution path	Target audience: Healthcare Professionals (HCPs) Educational material is to be distributed directly to HCPs via national routes. HCPs are to guide the patient about the risks and measures associated with mycophenolate before initiating or continuing treatment with mycophenolate.
Plans for evaluating the effectiveness of the interventions and criteria for success	How effectiveness of risk minimization measures for the safety concern will be measured: **Process Indicator:** The extent of distribution of educational material by the MAH in all countries in the EEA. **Outcome indicator:** The incidence of adverse pregnancy outcomes, as evident in the literature and/or inferred from the rate of adverse event reports in association with pregnancy and mycophenolate

	Criteria for judging the success of the proposed risk minimization measures: Criteria for judging success depends upon the overall frequency of adverse pregnancy outcomes and harms that are associated with pregnancy. Planned dates for assessment: Process (distribution) is measured once a year at the DLP-1 month. Outcome is measured on an on-going basis via signal detection and presented in each scheduled PSUR (PBRER) for CellCept.
DLP = data lock point; EEA = European Economic Area; HCP = healthcare professional; MAH = marketing authorization holder;PBRER = periodic benefit risk evaluation report.	

Additional risk-minimization measure	**Educational Guide for Patients**
Objective(s)	The educational materials are intended to communicate key safety messages to patients or their parents receiving mycophenolate mofetil, and to provide patients with important safety information. The objective is to minimize the number of pregnancies exposed to MMF.
Rationale for the additional risk-minimization activity	Mycophenolate is a powerful human teratogen. Spontaneous abortion and congenital malformations have been reported following mycophenolate exposure during pregnancy. Therefore, CellCept is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Physicians should ensure that women taking mycophenolate understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.
Target audience and planned distribution path	Target audience: Healthcare Professionals (HCPs) Patients Educational material is to be distributed directly to HCPs via national routes. HCPs are to guide the patient about the risks and measures associated with mycophenolate before initiating or continuing treatment with mycophenolate.
Plans for evaluating the effectiveness of the interventions and criteria for success	How effectiveness of risk minimization measures for the safety concern will be measured: **Process Indicator:** The extent of distribution of educational material by the MAH in all countries in the EEA. **Outcome indicator:** The incidence of adverse pregnancy outcomes, as evident in the literature and/or inferred from the rate of adverse event reports in association with pregnancy and mycophenolate Criteria for judging the success of the proposed risk minimization measures: Criteria for judging success depends upon the overall frequency of adverse pregnancy outcomes and harms that are associated with pregnancy.

	Planned dates for assessment: Process (distribution) is measured once a year at the DLP-1 month. Outcome is measured on an on-going basis via signal detection and presented in each scheduled PSUR (PBRER) for CellCept.

EEA=European Economic Area; HCP=Healthcare Professional; MAH=Marketing Authorization Holder; MMF=mycophenolate mofetil; PSUR=Periodic Safety Update Report; PBRER=Periodic Benefit-Risk Evaluation Report.

V.3 SUMMARY OF RISK-MINIMIZATION MEASURES

Table 11 Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Pregnancy Adverse Effects including Teratogenicity and Mutagenicity	**Routine risk communication:** • Section 4.3 of the EU SmPC Contraindications • Section 4.4 of the EU SmPC Special warnings and precautions for use • Section 4.6 Pregnancy & Lactation • Section 4.8 of the EU SmPC: Undesirable effects **Legal status:** CellCept is a prescription only medicine **Additional risk minimization measures:** HCP Guide Patient Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None

EU SmPC=European Union Summary of Product Characteristics; HCP=Healthcare Professional.

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PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

Summary of Risk Management Plan for CellCept® (mycophenolate mofetil)

This is a summary of the risk-management plan (RMP) for CellCept®. The RMP details important risks of CellCept, how these risks can be minimized, and how more information will be obtained about CellCept's risks and uncertainties (missing information).

CellCept summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how CellCept should be used.

This summary of the RMP for CellCept 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 the CellCept RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

CellCept is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in *adult and paediatric (1 to 18 years of age)* patients receiving allogeneic renal, cardiac or hepatic transplants (see SmPC for the full indication).

It contains mycophenolate mofetil as the active substance, and it is given by oral and IV route.

Further information about the evaluation of CellCept benefits can be found in CellCept EPAR, including in its plain-language summary, available on the EMA Web site, under the medicine's Web page:

https://www.ema.europa.eu/en/medicines/human/EPAR/cellcept

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of CellCept together with measures to minimize such risks and the proposed studies for learning more about CellCept risks, are outlined below.

Measures to minimize 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 authorized pack size—The amount of medicine in a pack is chosen so as 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 minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of CellCept, these measures are supplemented with *additional risk-minimization* measures mentioned under relevant risks below.

In addition to these measures, information about AEs is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of CellCept are risks that need special risk-management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. 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 CellCept. 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 about 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	Adverse pregnancy outcomes including teratogenicity and mutagenicity
Important potential risks	None
Missing Information	None

II.B Summary of Important Risks

Important Identified Risk: Adverse pregnancy outcomes including teratogenicity and mutagenicity	
Evidence for linking the risk to the medicine	Pre-clinical data and spontaneous cases reported in the post-marketing setting have both demonstrated that exposure of pregnancies to CellCept may lead to adverse outcomes.
Risk factors and risk groups	Women of childbearing potential and women who are breast feeding.

Risk-minimization measures	**Routine risk-minimization measures**: inclusion of safety concern in all product labels and patient information leaflets **Additional risk-minimization measures:** HCP Guide and Patient Guide
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

HCP = Healthcare Professional.

II.C Post-Authorization Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorization

There are no studies that are conditions of the marketing authorization or specific obligation of CellCept. Annual safety reports to further characterize the missing information of long term safety in pediatric population is planned.

II.C.2 Other Studies in Post-Authorization Development Plan

There are no studies required for CellCept.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

None

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES

Prior to the use of CellCept® in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials and any other aspects of the program, with the National Competent Authority.

The educational program is aimed at reducing the number of pregnancies exposed to CellCept.

The MAH shall ensure that in each Member State where CellCept is marketed, all healthcare professionals and patients who are expected to prescribe and use CellCept have access to/are provided with the following educational messages to be disseminated through professional bodies:

- HCP Guide
- Patient Guide

TABLE OF CONTENTS

1. HEALTHCARE PROFESSIONALS

1.1 GUIDE FOR HEALTHCARE PROFESSIONALS

This guide has been designed to highlight the risks to babies associated with exposure to mycophenolate mofetil during pregnancy and to minimise the number of pregnancies during treatment with this medicinal product. This guide provides background information on the teratogenicity and mutagenicity of mycophenolate mofetil in humans and it gives details about the nature and magnitude of the risk, in line with the information provided in the SmPC. This guide helps the treating physician or Healthcare professional (HCP) to ensure that women and men taking mycophenolate mofetil understand the risk of harm to the foetus, the need for effective contraception, and the need to immediately consult them if there is a possibility of pregnancy. In particular, this guide helps physician/HCP so that they:

- Counsel patients at risk to make sure they understand the risks and the measures required to minimise them.
- Provide female and male patients at risk with the CellCept Guide for Patients and address any questions or concerns they might have.
- Explain the importance, methods, and timing of pregnancy tests prior and during treatment with mycophenolate mofetil.
- Advise patients before initiating treatment with mycophenolate mofetil, women of childbearing potential to undergo a pregnancy test to ensure there is no unintended exposure of the embryo to mycophenolate mofetil. Two serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL are recommended; the second test should be performed 8 to 10 days after the first one and immediately before starting mycophenolate mofetil. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to promptly consult their physician if pregnancy occur.
- Provide counselling on the use of effective contraception prior to and during the entire duration of treatment with mycophenolate mofetil and for 6 weeks (female patients) or 90 days (male patients), after they stop taking mycophenolate mofetil.
- Advise patients taking mycophenolate mofetil that they must let the physician/HCP know in advance if they are considering becoming pregnant or fathering a child so that the physician/HCP can discuss possible treatment alternatives with them.
- Advise patients treated with mycophenolate mofetil not to donate blood during or for 6 weeks after stopping treatment. Male patients should not donate semen during therapy or for 90 days after stopping treatment.
- Advise patients that this medicine is for their own personal use, they should not give it to anyone else, and should return any unused medicine to their pharmacist at the end of treatment.
- Advise patients on action if a pregnancy occurs or is suspected during or shortly after being treated with mycophenolate mofetil. Patients will be informed that they

should not stop taking mycophenolate mofetil but must contact their doctor immediately. It will be explained that the correct course of action, based on an assessment of the individual benefit-risk, will be determined on a case-by-case basis through a discussion between the treating physician and the patient.

Although this guide presents important information concerning the adverse pregnancy outcomes associated with mycophenolate mofetil, please consult the CellCept Summary of Product Characteristics (SmPC) for full information on mycophenolate mofetil. In addition, a pregnancy follow-up questionnaire including details of exposure during pregnancy, including timing and dose, duration of therapy, before and during pregnancy, concomitant drugs, known teratogenic risks and full details of congenital malformations should be agreed to with the national competent authorities.

2. PATIENTS/CARERS

2.1 PATIENT/CARER GUIDE

The CellCept (mycophenolate mofetil) Guide for Patients informs patients about the risks of mycophenolate mofetil for the unborn baby, and the ways to reduce those risks.

- If patients are treated with CellCept or other products containing mycophenolate mofetil, and if they can get pregnant, their doctor will inform them about the risks of mycophenolate mofetil for the unborn baby.
- Their doctor will talk about birth control and pregnancy planning and will answer any questions patient's may have on this subject.
- This guide will help the patient to remember the information that has been discussed with their doctor. Thus, patients should keep the patient/carer guide with them so that they can refer to it again, if needed.
- In addition to reading this guide, it is also important that patients read the package leaflet supplied with the medicine for full information on mycophenolate mofetil and discuss with their doctor if they have any questions or concerns about the risks of mycophenolate mofetil.

Details of the key elements of Patient Guide:

- Mycophenolate mofetil causes birth defects and miscarriage.
- For a woman who could become pregnant, they must provide a negative pregnancy test before starting treatment.
- For men and women treated with mycophenolate mofetil, they must follow the contraceptive advice given to them by their doctor.
- If patients do not fully understand the information that has been given to them, they can check with their doctor to explain it again before they take mycophenolate mofetil.
- Do NOT stop taking mycophenolate mofetil without talking to the doctor.

- This medicine is just for patients - do not give it to other people because it may be harmful to them.

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