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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	CellCept	mycophenolate mofetil (MMF).	Indications / Uses	Revision of text to read "CellCept is indicated in combination with corticosteroids and ciclosporin for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants."	13/12/2021	Roche
			Dosage / Administration	Revision of text to read "Please refer to the full prescribing information for corticosteroids and ciclosporin, which are used in combination with CellCept. The first CellCept dose should be administered as soon as possible after renal, cardiac or hepatic transplantation. The solution for infusion may be used in renal and hepatic transplantation instead of the oral forms over a period of up to 14 days. The administration of CellCept capsules or film-coated tablets should begin as soon as oral medication of the patient is possible"		
				"Revision of text to read under the sub heading Intravenous administration "Caution: CellCept i.v. solution must not be intravenously administered by rapid infusion or bolus injection"		
				Revision of text to read under the sub heading Renal and Hepatic transplant " Adults: The recommended dose for renal and hepatic transplant patients is 1 g twice daily (daily dose 2 g). The first dose of CellCept i.v. should be given within 24 hours after transplantation. After reconstitution as a 6 mg/ml solution, CellCept i.v. must be administered by slow intravenous infusion over at least 2 hours into a peripheral or central vein (infusion pump). The suitable infusion rate is 84 ml/hour. In renal transplant rejection, dose reduction or discontinuation is unnecessary. No pharmacokinetic data are available in hepatic transplant rejection."		

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	CellCept	mycophenolate mofetil (MMF).	Dosage / Administration	Revision of text to read under the sub heading oral administration "Renal transplant, Adults: The best therapeutic benefit-risk ratio is observed with a daily dose of 2 g (4 capsules or 2 film-coated tablets twice daily). A daily dose of 2 g is generally recommended for renal transplant patients. Where a higher level of immunosuppression appears warranted in selected patients, a daily CellCept dose of 3 g (6 capsules or 3 film-coated tablets twice daily) can be given."	13/12/2021	Roche
				Revision of text under the sub heading Renal transplant children and adolescents (age 3 months to 18 years): "The recommended dose of mycophenolate mofetil is 600 mg/m2 administered orally twice daily (up to a maximum daily dose of 2 g). When the solid oral dosage forms are used, patients with a body surface area of 1.25 to 1.5 m2 may be treated with CellCept capsules at a dose of 750 mg twice daily (daily dose: 1.5 g). Patients with a body surface area >1.5 m2 may be treated with CellCept capsules or film-coated tablets at a dose of 1 g twice daily (daily dose 2 g)."		
				Revision of text to read under the sub heading cardiac transplant Adult "The recommended dose for cardiac transplant patients is 1.5 g twice daily (daily dose 3 g). In cardiac transplant rejection there is no reason for dose correction."		
				Revision of text to read under the sub heading hepatic transplant adults "The recommended dose for hepatic transplant patients is 1.5 g twice daily (daily dose 3 g). No pharmacokinetic data are available in hepatic transplant rejection."		

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	CellCept	mycophenolate mofetil (MMF)	Dosage / Administration	Revision of text to read under the sub heading clinical experience "The safety profile of CellCept in patients treated for refractory renal transplant rejection was similar to that observed in the pivotal studies for prevention of renal transplant rejection at a daily dose of 3 g. The main adverse events reported more frequently in patients receiving CellCept than in patients on IV. corticosteroids were diarrhoea and leukopenia, followed by anaemia, nausea, abdominal pain, sepsis, nausea with vomiting, and dyspepsia."	13/12/2021	Roche
				Revision of text to red under the sub heading clinical experinence in childern and adolescents (3months to 18 years) "In a clinical study with 100 pediatric patients aged 3 months to 18 years treated orally with mycophenolate mofetil 600 mg/m2 twice daily, the side effects were generally similar in type to those observed in adult patients receiving CellCept 1 g twice daily. However, the following treatment-related side effects occurred in children and adolescents at an incidence greater than 10% and were more frequent in children and adolescents, particularly in those under 6 years, than in adults: diarrhea, leukopenia, sepsis, infections, anemia."		
				Revision of text to read under the sub heading Elderly patients (≥65 years) "Elderly patients (≥65 years) may be at higher risk of adverse reactions due to immunosuppression, especially if they take CellCept as part of an immunosuppressive combination therapy. These patients may be at increased risk of certain infections (including cytomegalovirus [CMV] tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger persons."		

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	CellCept	mycophenolate mofetil (MMF)	Properties Effects	Revision of text to read under the sub heading clinical efficacy renal transplant adult "The primary efficacy endpoint was the proportion of patients in each treatment group with treatment failure within the first 6 months after transplantation (biopsy-proven acute rejection or death, graft loss or early termination from the study for other reasons). CellCept in combination with corticosteroids and ciclosporin led to a statistically significant decrease ($p < 0.05$) in the incidence of treatment failure within the first 6 months post-transplant compared to the active control with azathioprine:"	13/12/2021	Roche
				Revision of text under the sub heading clinical efficacy renal transplant pediatrics "The combined incidence of graft loss (5%) and patient death (2%) at 12 months post-transplant was also similar to that in adult renal transplant patients."		
				Revision of text to read under the sub heading clinical efficacy cardiac transplant "CellCept and azathioprine in either primary endpoint: (1) biopsy-proven rejection with hemodynamic compromise, retransplantation or death (32% on CellCept vs 35% on azathioprine), and (2) graft survival (death or retransplantation) in the first 12 months (6.2% on CellCept vs 11.4% on azathioprine)."		

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	CellCept	mycophenolate mofetil (MMF)	Properties Effects	Revision of text to read under the sub heading clinical efficacy hepatic transplant "The primary efficacy endpoints were: (1) the proportion of patients who experienced one or more episodes of biopsy-proven and treated rejection or death/retransplantation in the first 6 months post-transplant, and (2) the proportion of patients who experienced graft loss (death/retransplantation) during the first 12 months post-transplant. Patients who prematurely discontinued treatment were followed for rejection episodes and organ loss (death/retransplantation) for one year. Results: In the primary (intent-to-treat) analyses, CellCept in combination with corticosteroids and ciclosporin was more effective than azathioprine in preventing acute rejection (38.5% vs 47.7%; p=0.025) and equivalent to azathioprine for survival (death or retransplantation at 12 months: 14.7% vs 14.6%)."	13/12/2021	Roche
2	Concerta	Methylphenidate hydrochloride.	Undesirable effect	Deletion of texts under psychiatric disorder that read "Anorexia, Depression."Addition of texts under hepatobiliary disorders to include "Common: Alanine aminotransferase increased; uncommon: Hepatic enzyme increased; very rare: including acute hepatic failure and hepatic , Blood phosphatase increased, Blood bilirubin increased".Deletion of texts under investigations that read "Common: Alanine aminotransferase increased; uncommon: Hepatic enzyme increased; very rare: including acute hepatic failure and hepatic , Blood phosphatase increased, Blood bilirubin increased".	2/2/2022	Janssen
3	Forxiga	Dapagliflozin	Therapeutic indications	Addition of texts to include "chronic kidney disease: Forxiga is indicated in adults for the treatment of chronic kidney disease"	1/2/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Forxiga	Dapagliflozin	Posology and method of administration	Addition of texts under posology to include "chronic kidney disease:The recommended dose is 10mg dapagliflozin once daily.In the DAPA-CKD study, dapagliflozin was administered in conjunction with other chronic kidney disease therapies (see Pharmacodynamic properties)."	1/2/2022	Roche
			Special warnings and precautions for use	Revision of texts under special populations, renal impairment to read " Renal impairment: No dose adjustment is required based on renal function. Due to limited experience, it is not recommended to initiate treatment with dapagliflozin in patients with GFR < 25 mL/min. In patients with diabetes mellitus, the glucose lowering efficacy of dapagliflozin is a when the glomerular filtration rate (GFR) is 45 mL/min and is likely absent in patients with severe renal impairment. Therefore, if GFR falls below 45 mL/min, additional glucose lowering treatment should be considered in patients with diabetes mellitus if further glycaemic control is needed		
				Addition of texts under renal impairment to include "Due to limited experience, it is not recommended to initiate treatment with dapagliflozin in patients with GFR < 25 mL/min."		
3	Forxiga	Dapagliflozin	Special warnings and precautions for use	Revision of texts under renal impairment to read " The glucose lowering efficacy of dapagliflozin is dependent on renal function and is reduced in patients with GFR < 45 mL/min and is likely absent in patients with severe renal impairment (see Posology and method of administration, Pharmacodynamic properties and Pharmacokinetic properties). In one study in patients with type 2 diabetes mellitus with moderate renal impairment (GFR < 60 mL/min), a higher proportion of patients treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo.	1/2/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Forxiga	Dapagliflozin	Special warnings and precautions for use	Addition of texts under Necrotising fasciitis of the perineum to read " Necrotising fasciitis of the perineum (Fournier's gangrene):Postmarketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors (see Undesirable effects). This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Forxiga should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted	1/2/2022	Roche
3	Forxiga	Dapagliflozin	Special warnings and precautions for use	Revision of texts under renal impairment to read " The glucose lowering efficacy of dapagliflozin is dependent on renal function and is reduced in patients with GFR < 45 mL/min and is likely absent in patients with severe renal impairment (see Posology and method of administration, Pharmacodynamic properties and Pharmacokinetic properties). In one study in patients with type 2 diabetes mellitus with moderate renal impairment (GFR < 60 mL/min), a higher proportion of patients treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo.	1/2/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Forxiga	Dapagliflozin	Special warnings and precautions for use	Addition of texts under Necrotising fasciitis of the perineum to read " Necrotising fasciitis of the perineum (Fournier's gangrene):Postmarketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors (see Undesirable effects). This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Forxiga should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted	1/2/2022	Roche
			Undesirable effects	Addition of texts under Chronic kidney disease to include " Chronic kidney disease: There is no experience with dapagliflozin for the treatment of chronic kidney disease in patients without diabetes who do not have albuminuria. Patients with albuminuria may benefit more from treatment with dapagliflozin.		
3	Forxiga	Dapagliflozin	Undesirable effects	Addition of texts to read "chronic kidney diseaseIn the dapagliflozin renal outcome study in patients with chronic kidney disease (DAPA-CKD), 2,149 patients were treated with dapagliflozin 10 mg and 2,149 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, with eGFR ≥ 25 to ≤ 75 mL/min/1.73 m2, and albuminuria (urine albumin creatinine ratio [UACR] ≥ 200 and ≤ 5000 mg/g). Treatment was continued if eGFR fell to levels below 25 mL/min/1.73 m2.The overall safety profile of dapagliflozin in patients with chronic kidney disease was consistent with the known safety profile of dapagliflozin.	1/2/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
				Addition of texts under infections and infestations to read " Very rare-Necrotising fasciitis of the perineum (Fournier's gangrene)		
3	Forxiga	Dapagliflozin	Undesirable effects	Addition of texts under Vulvovaginitis, balanitis and related genital infections to read "In the DAPA-CKD study, there were 3 (0.1%) patients with serious adverse events of genital infections in the dapagliflozin group and none in the placebo group. There were 3 (0.1%) patients with adverse events leading to discontinuation due to genital infections in the dapagliflozin group and none in the placebo group. Serious adverse events of genital infections or adverse events leading to discontinuation due to genital infections were not reported for any patients without diabetes" Addition of texts under Necrotising fasciitis of the perineum (Fournier's gangrene) to read "Cases of Fournier's gangrene have been reported postmarketing in patients taking SGLT2 inhibitors, including dapagliflozin (see Special warnings and precautions for use). In the DECLARE study with 17,160 type 2 diabetes mellitus patients and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported, one in the dapagliflozin-treated group and 5 in the placebo group.	1/2/2022	Roche
3	Forxiga	Dapagliflozin	Undesirable effects	Addition of texts under Hypoglycaemia to read "In the DAPA-CKD study, major events of hypoglycaemia were reported in 14 (0.7%) patients in the dapagliflozin group and 28 (1.3%) patients in the placebo group and observed only in patients with type 2 diabetes mellitus. "	1/2/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
				Addition of texts under Volume depletion to read " In the DAPA-CKD study, the numbers of patients with events suggestive of volume depletion were 120 (5.6%) in the dapagliflozin group and 84 (3.9%) in the placebo group. There were 16 (0.7%) patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group and 15 (0.7%) patients in the placebo group.		
				Addition of texts under Diabetic Ketoacidosis to read "In the DAPA-CKD study, events of DKA were not reported in any patient in the dapagliflozin group and in 2 patients with type 2 diabetes mellitus in the placebo group.		
3	Forxiga	Dapagliflozin	Undesirable effects	Addition of texts under Urinary tract infections to read "In the DAPA-CKD study, the numbers of patients with serious adverse events of urinary tract infections were 29 (1.3%) in the dapagliflozin group and 18 (0.8%) in the placebo group. There were 8 (0.4%) patients with adverse events leading to discontinuations due to urinary tract infections in the dapagliflozin group and 3 (0.1%) in the placebo group. The numbers of patients without diabetes reporting serious adverse events of urinary tract infections or adverse events leading to discontinuation due to urinary tract infections were similar between treatment groups (6 [0.9%] versus 4 [0.6%] for serious adverse events, and 1 [0.1%] versus 0 for adverse events leading to discontinuation, in the dapagliflozin and placebo groups, respectively)	1/2/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Forxiga	Dapagliflozin	Undesirable effects	Addition of texts under Increased creatinine to read "In the DAPA-CKD study, eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial (day 14) decrease in mean eGFR was -4.0 mL/min/1.73 m2 in the dapagliflozin group and -0.8 mL/min/1.73 m2 in the placebo group. At 28 months, change from baseline in eGFR was -7.4 mL/min/1.73 m2 in the dapagliflozin group and -8.6 mL/min/1.73 m2 in the placebo group.	/2/2022	Roche
			Pharmacological Properties	Revision of texts under mechanism of action to read "This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and preserve renal function. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF and DAPA-CKD studies."		
4	Forxiga	Dapagliflozin	Clinical Particulars, Therapeutic Indications	Revision of text under the heading Type 2 diabetes mellitus to read as "For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see Special warnings and precautions for use, Interaction with other medicinal products and other forms of interaction and Pharmacodynamic properties" Addition of a heading to read " Chronic kidney disease" under the subsection Therapeutic indications. Addition of the text to read "Forxiga is indicated in adults for the treatment of chronic kidney disease." under the heading Chronic kidney disease.	25/01/22	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
			Posology and method of administration, Posology	Addition of the heading to read "Chronic kidney disease" under the subsection Posology.Addition of the text to read "The recommended dose is 10mg dapagliflozin once daily. In the DAPA-CKD study, dapagliflozin was administered inconjunction with other chronic kidney disease therapies (seePharmacodynamic properties)." under the heading Chronic kidney disease.		
4	Forxiga	Dapagliflozin	Posology and method of administration, Special populations, Renal impairment	Revision of the subsection under the section Posology and method of administration, Special populations, Renal impairment to read as "Renal impairment"Revision of text to read "No dose adjustment is required based on renal function. Due to limited experience, it is not recommended to initiate treatmentwith dapagliflozin in patients with GFR < 25 mL/min. In patients with diabetes mellitus, the glucose lowering efficacy of dapagliflozin reduced when the glomerular filtration rate (GFR) is <45 mL/min and is likely absent in patients with severe renal impairment. Therefore, if GFR falls below 45 mL/min, additional glucose lowering treatment should be considered in patients with diabetes mellitus if further glycaemic control is needed (see Special warnings and precautions for use, Undesirable effects, Pharmacodynamic properties andPharmacokinetic properties)"Deletion of the subsection "Treatment of heart failure in patients with renal impairment" under the section Posology and method of administration, Special populations, Renal impairmentDeletion of the text "No dose adjustment is required based on renal function (see Special warnings and precautions for use). There is limited experience with dapagliflozin for the treatment of heart failure in patients with severe renal impairment (GFR < 30 mL/min). " under the subsection Treatment of heart failure in patients with renal impairment.	25/01/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Forxiga	Dapagliflozin	Special warnings and precautions for use, Renal impairment	Revision of text under the subsection Renal impairment to read as " Due to limited experience, it is not recommended to initiate treatment with dapagliflozin in patients with GFR < 25 mL/min. The glucose lowering efficacy of dapagliflozin is dependent on renal function and is reduced in patients with GFR < 45 mL/min and is likely absent in patients with severe renal impairment (see Posology andmethod of administration, Pharmacodynamic properties and Pharmacokinetic properties). In one study in patients with type 2 diabetes mellitus with moderate renal impairment (GFR < 60 mL/min), a higher proportion of patients treatedwith dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo"Deletion of the subsection "Treatment of heart failure" under the section Special warnings and precautions for use, Renal impairment.Deletion of the text " There is limited experience with dapagliflozin for the treatment of heart failure in patients with severe renal impairment(GFR < 30 mL/min). In patients treated with dapagliflozin for both heart failure and type 2 diabetes mellitus, additional glucose-lowering treatment should beconsidered if GFR falls persistently below 45 mL/min." under the subsection Treatment of heart failure	25/01/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Forxiga	Dapagliflozin	Special warnings and precautions for use, Necrotising fasciitis of the perineum	Addition of a subsection to read "Necrotising fasciitis of the perineum (Fournier's gangrene)" under the section Special warnings and precautions for use, Necrotisingfasciitis of the perineum.Addition of the text to read " Postmarketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors (see Undesirable effects). This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment. Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Forxiga should be discontinued, and prompt treatment (including antibiotics and surgical debridement) should be instituted." under the subsection Necrotising fasciitis of the perineum (Fournier's gangrene)	25/01/22	Roche
			Special warnings and precautions for use, Chronic kidney disease	Addition of the subsection "Chronic kidney disease" under the section Special warnings and precautions for use, Chronic kidney disease. Addition of the text " There is no experience with dapagliflozin for the treatment of chronic kidney disease in patients without diabetes who do not have albuminuria. Patients with albuminuria may benefit more from treatment with dapagliflozin." under the subsection Chronic kidney disease.		

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Forxiga	Dapagliflozin	Undesirable effects, Summary of the safety profile	Addition of the heading "Chronic kidney disease" under the subsection Summary of safety profile.Addition of text to read " In the dapagliflozin renal outcome study in patients with chronic kidney disease (DAPA-CKD), 2,149 patients were treated with dapagliflozin 10 mg and 2,149 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, with eGFR ≥ 25 to ≤ 75 mL/min/1.73 m2, and albuminuria (urine albumin creatinine ratio [UACR] ≥ 200 and ≤ 5000 mg/g). Treatment was continued if eGFR fell to levels below 25 mL/min/1.73 m2. The overall safety profile of dapagliflozin in patients with chronic kidney disease was consistent with the known safety profile of dapagliflozin." under the heading Chronic kidney disease.	25/01/2022	Roche
			Undesirable effects, Tabulated list of adverse reactions	Addition of the column " Very rare" to the table under the subsection Adverse reactions in placebo-controlled clinical studies and postmarketing experience. Addition of a very rare adverse reaction" Necrotising fasciitis of the perineum (Fournier's gangrene) b,i" under the system organ class Infections and infestations.		
4	Forxiga	Dapagliflozin	Undesirable effects, Description of selected adverse reactions, Vulvovaginitis, balanitis and related genital infections	Addition of text to read "In the DAPA-CKD study, there were 3 (0.1%) patients with serious adverse events of genital infections in the dapagliflozin group and none in the placebo group. There were 3 (0.1%) patients with adverse events leading to discontinuation due to genital infections in the dapagliflozin group and none in the placebo group. Serious adverse events of genital infections or adverse events leading to discontinuation due to genital infections were not reported for any patients without diabetes." under the subsection Vulvovaginitis, balanitis and related genital infections.	25/01/22	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
			Undesirable effects, Description of selected adverse reactions, Necrotising fasciitis of the perineum	Addition of the subsection " Necrotising fasciitis of the perineum (Fournier's gangrene) " under the section Undesirable effects, Description of selected adverse reactions, Necrotising fasciitis of the perineum. Addtion of text to read " Cases of Fournier's gangrene have been reported postmarketing in patients taking SGLT2 inhibitors, including dapagliflozin (see Special warnings and precautions for use). In the DECLARE study with 17,160 type 2 diabetes mellitus patients and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported, one in the dapagliflozin-treated group and 5 in the placebo group." under the subsection Necrotising fasciitis of the perineum (Fournier's gangrene)		
4	Forxiga	Dapagliflozin	Undesirable effects, Description of selected adversereactions, Hypoglycaemia	Addition of text to read " In the DAPA-CKD study, major events of hypoglycaemia were reported in 14 (0.7%) patients in the dapagliflozin group and28 (1.3%) patients in the placebo group and observed only in patientswith type 2 diabetes mellitus." under the subsection Hypoglycaemia	25/01/22	Roche
			Undesirable effects, Description of selected adverse reactions, Volume depletion	Addition of text to read "In the DAPA-CKD study, the numbers of patients with events suggestive of volume depletion were 120 (5.6%) in the dapagliflozin group and 84 (3.9%) in the placebo group. There were 16 (0.7%) patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group and 15 (0.7%) patients in the placebo group. " under the subsection Volume depletion.		

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Forxiga	Dapagliflozin	Undesirable effects, Description of selected adversereactions, Diabetic Ketoacidosis	Addition of text to read " In the DAPA-CKD study, events of DKA were not reported in any patient in the dapagliflozin group and in 2 patients with type 2diabetes mellitus in the placebo group." under the subsection Diabetic ketoacidosis in type 2 diabetes mellitus	25/01/22	Roche
			Undesirable effects, Description of selected adverse reactions, Urinary tract infections	Addition of text to read " In the DAPA-CKD study, the numbers of patients with serious adverse events of urinary tract infections were 29 (1.3%) in the dapagliflozin group and 18 (0.8%) in the placebo group. There were 8 (0.4%) patients with adverse events leading to discontinuations due to urinary tract infections in the dapagliflozin group and 3 (0.1%) in the placebo group. The numbers of patients without diabetes reporting serious adverse events of urinary tract infections or adverse events leading to discontinuation due to urinary tract infections were similar between treatment groups (6 [0.9%] versus 4 [0.6%] for serious adverse events, and 1 [0.1%] versus 0 for adverse events leading to discontinuation, in the dapagliflozin and placebo groups, respectively)."under the subsection Urinary tract infections		
4	Forxiga	Dapagliflozin	Undesirable effects, Description of selected adversereactions, Increased creatinine	Addition of text to read “In the DAPA-CKD study, eGFR decreased over time in both thedapagliflozin group and the placebo group. The initial (day 14)decrease in mean eGFR was -4.0 mL/min/1.73 m2 in the dapagliflozingroup and -0.8 mL/min/1.73 m2 in the placebo group. At 28 months,change from baseline in eGFR was -7.4 mL/min/1.73 m2 in thedapagliflozin group and -8.6 mL/min/1.73 m2 in the placebo group." under the subsection Increased creatinine	25/01/22	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Forxiga	Dapagliflozin	Pharmacological Properties, Pharmacodynamicproperties, Mechanism of action	Revision of text under the subsection mechanism of action to read " Dapagliflozin is a highly potent (Ki: 0.55 nM), selective and reversibleinhibitor of sodium-glucose co-transporter 2 (SGLT2).Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucosefrom the glomerular filtrate in the proximal renal tubule with aconcomitant reduction in sodium reabsorption leading to urinaryexcretion of glucose and osmotic diuresis. Dapagliflozin thereforeincreases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduce intraglomerularpressure. This combined with osmotic diuresis leads to a reduction involume overload, reduced blood pressure, and lower preload andafterload, which may have beneficial effects on cardiac remodelling and preserve renal function. Other effects include an increase in haematocrit and reduction in body weight. The cardiac and renalbenefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes asdemonstrated in the DAPA-HF and DAPA-CKD studies."	25/01/22	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Forxiga	Dapagliflozin	Pharmacological Properties, Pharmacodynamicproperties, Clinical efficacy and safety	Revision of text under the heading Type 2 diabetes mellitus to read " Improvement of glycaemic control and reduction ofcardiovascular and renal morbidity and mortality are an integralparts of the treatment of type 2 diabetes"Revision of text under the heading Cardiovascular and renal outcomes to read as " At baseline, 10.0% of patients had a history of heart failure. MeaneGFR was 85.2 mL/min/1.73 m2, 7.4% of patients had eGFR < 60mL/min/1.73 m2, and 30.3% of patients had micro- or macroalbuminuria (UACR ≥ 30 to ≤ 300 mg/g or > 300 mg/g, respectively).Figure 2 , Figure 2 footnote and Nephropathy sections…severalupdates to End stage kidney renal disease and ESKD"Revision of text to read " Patients were on standard of care therapy; 94% of patients were treated with ACE-I, ARB or angiotensin receptor-neprilysin inhibitor (ARNI, 11%), 96% with beta-blocker, 71% with mineralocorticoidreceptor antagonist (MRA), 93% with diuretic and 26% had animplantable device (with defibrillator function)." under the heading Heart failure.Addition of subsection to read "Chronic kidney disease " under the section Pharmacological Properties, Pharmacodynamicproperties, Clinical efficacy and safety.Addition of text to read " The Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (DAPA-CKD) was an international, multicentre, randomised, double blind, placebo-controlled study in patients with chronic kidneydisease (CKD) with eGFR ≥ 25 to ≤ 75 mL/min/1.73 m2 andalbuminuria (UACR ≥ 200 and ≤ 5000 mg/g) to determine the effect ofdapagliflozin compared with placebo, when added to backgroundstandard of care therapy, on the incidence of the composite endpointof ≥ 50% sustained decline in eGFR, end-stage kidney disease (ESKD)(defined as sustained eGFR < 15 mL/min/1.73 m2, chronic dialysistreatment or receiving a renal transplant), cardiovascular or renal death.Of 4,304 patients, 2,152 were randomised to dapagliflozin 10 mg and2,152 to placebo and followed for a median of 28.5 months.Treatment was continued if eGFR fell to levels below 25 mL/min/1.73 m2 during the study and	25/01/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
				could be continued in cases when dialysiswas needed.The mean age of the study population was 61.8 years, 66.9% weremale. At baseline, mean eGFR was 43.1 mL/min/1.73 m2 and medianUACR was 949.3 mg/g, 44.1% of patients had eGFR 30 to < 45mL/min/1.73 m2 and 14.5% had eGFR < 30 mL/min/1.73 m2. 67.5%of the patients had type 2 diabetes mellitus. Patients were onstandard of care (SOC) therapy; 97.0% of patients were treated withan angiotensin-converting enzyme inhibitor (ACEi) or angiotensinreceptor blocker (ARB).The study was stopped early for efficacy prior to the planned analysisbased on a recommendation by the independent Data MonitoringCommittee. Dapagliflozin was superior to placebo in preventing theprimary composite endpoint of ≥ 50% sustained decline in eGFR,reaching end-stage kidney disease, cardiovascular or renal death.Based on the Kaplan-Meier plot for the time to first occurrence of theprimary composite endpoint, the treatment effect was evidentbeginning at 4 months and was maintained through the end of study(Figure 5)." under the subsection Chronic kidney disease.Addition of the heading to read " Figure 5: Time to first occurrence of the primary composite endpoint, ≥ 50% sustained decline in eGFR, end-stage kidneydisease, cardiovascular or renal death" under the subsection Chronic kidney disease.Addition of a graph of "Patients with event (%) against Months from randomisation"Addition of text to read " All four components of the primary composite endpoint individuallycontributed to the treatment effect. Dapagliflozin also reduced theincidence of the composite endpoint of ≥50% sustained decline ineGFR, end-stage kidney disease or renal death and the compositeendpoint of cardiovascular death and hospitalisation for heart failure.Treatment with dapagliflozin improved overall survival in chronickidney disease patients with a significant reduction in all-causemortality (Figure 6)." under Figure 5Addition of the heading to read as " Figure 6: Treatment effects for the primary and secondary compositeendpoints, their individual components, and all-cause mortality" under the subsection Chronic kidney diseaseAddition of a		

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
				table under the heading Figure 6: Treatment effects for the primary and secondary composite endpoints, their individual components, and all-cause mortality.Addition of text to read " The number of first events for the single components are the actual number of first eventsfor each component and does not add up to the number of events in the composite endpoint. Event rates are presented as the number of subjects with event per 100 patient years of follow-up. Hazard ratio estimates are not presented for subgroups with less than 15 events in total,both arms combined. The treatment benefit of dapagliflozin was consistent in chronic kidney disease patients with type 2 diabetes mellitus and withoutdiabetes. Dapagliflozin reduced the primary composite endpoint of≥ 50% sustained decline in eGFR, reaching end-stage kidney disease,cardiovascular or renal death with a HR of 0.64 (95% CI 0.52, 0.79) inpatients with type 2 diabetes mellitus and 0.50 (95% CI 0.35, 0.72) inpatients without diabetes. The treatment benefit of dapagliflozin over placebo on the primary endpoint was also consistent across other key subgroups, including eGFR, age, gender, and region." under the heading Figure 6: Treatment effects for the primary and secondary composite endpoints, their individual components, and all-cause mortality.Revision of text under the subsection Paediatric population to read as " The European Medicines Agency has waived the obligation to submit the results of studies with dapagliflozin in all subsets of the paediatric population in the prevention of cardiovascular events in patients with chronic heart failure and in the treatment of chronic kidney disease (see Posology and method of administration for information on paediatric use)."		

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Forxiga	Dapagliflozin	Pharmacological Properties, Pharmacokineticproperties, Special populations	Revision of text under the subsection Renal impartment to read " with type 2 diabetes mellitus and mild, moderate or severe renalimpairment (as determined by iohexol plasma clearance) had meansystemic exposures of dapagliflozin of 32%, 60% and 87% higher,respectively, than those of subjects with type 2 diabetes mellitus andnormal renal function. The steady-state 24-hour urinary glucoseexcretion was highly dependent on renal function and 85, 52, 18 and11 g of glucose/day was excreted by subjects with type 2 diabetesmellitus and normal renal function or mild, moderate or severe renalimpairment, respectively. The impact of haemodialysis ondapagliflozin exposure is not known. The effect of reduced renalfunction on systemic exposure was evaluated in a populationpharmacokinetic model. Consistent with previous results, modelpredicted AUC was higher in patients with chronic kidney diseasecompared with patients with normal renal function, and was notmeaningfully different in chronic kidney disease patients with type 2diabetes mellitus and without diabetes."	25/01/2022	Roche
5	MabThera(1400)	Rituximab	Fertility, pregnancy and lactation	Revision of text to read "Limited data on rituximab excretion into breast milk suggest very low milk levels (relative infant dose less than 0.4%). Few cases of follow-up of breastfed infants describe normal growth and development up to 1.5 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breastfeeding is not recommended while being treated with rituximab and optimally for 12 months following rituximab treatment." under Breast-feeding	17/01/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	MabThera(1400)	Rituximab	Pharmaceutical Particulars	Revision of text under the subsection Special precautions for disposal and other handling to read as "MabThera is provided in sterile, preservative-free, non-pyrogenic, single-use vials. Use a sterile needle and syringe to prepare MabThera. The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps: • Needles and syringes should never be reused.• Place all used needles and syringes into a sharps container (puncture-proof disposable container)."	17/01/2022	Roche
6	MabThera(1600)	Rituximab	Pharmaceutical Particulars	Revision of text under the subsection Special precautions for disposal and other handling to read as "MabThera is provided in sterile, preservative-free, non-pyrogenic, single-use vials. Use a sterile needle and syringe to prepare MabThera. The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps: • Needles and syringes should never be reused. • Place all used needles and syringes into a sharps container (puncture-proof disposable container)."	17/01/2022	Roche
6	MabThera(1600)	Rituximab	Fertility, pregnancy and lactation	Revision of text to read "Limited data on rituximab excretion into breast milk suggest very low milk levels (relative infant dose less than 0.4%). Few cases of follow-up of breastfed infants describe normal growth and development up to 1.5 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breastfeeding is not recommended while being treated with rituximab and optimally for 12 months following rituximab treatment." under Breast-feeding	17/01/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Madopar	Levodopa + benserazide	Indications / Uses	Deletion of the text "Madopar HBS is indicated for all types of fluctuations in treatment response, in particular those related to plasma concentrations (for example, post-dose dyskinesia or end-of-dose akinesia), and for better control of nocturnal symptoms".	17/01/2022	Roche
7	Madopar	Levodopa + benserazide	Dosage/Administration	Addition of the text "Madopar HBS is indicated for all types of fluctuations in treatment response, in particular those related to plasma concentrations (for example, post-dose dyskinesia or end-of-dose akinesia), and for better control of nocturnal symptoms. Further experience will show whether it is advantageous to use Madopar HBS from the outset in Parkinson patients not previously treated with levodopa alone or in combination with a decarboxylase inhibitor in conventional form." under Parkinson's disease	17/01/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Madopar	Levodopa + benserazide	Special dosage instructions	Addition of the text "Patients who experience large fluctuations in the medicine's effect in the course of the day ("on-off" phenomena) should receive smaller, more frequent single doses. Parkinsonian patients should be informed that their condition may temporarily deteriorate. Patients who experience large fluctuations in response during the day ("on-off" phenomena) should receive smaller, more frequent doses or be switched tosustained-release formulations of Madopar.Patients who experience large fluctuations in the medicine's".Addition of text "Patients should be informed that their conditionmay temporarily deteriorate".Addition of text "Excessive responses to treatment (dyskinesia) should be controlled by increasing the interval between doses rather than reducing the single doses. Treatment with standard Madopar or water-soluble Madopar should be resumed if the response to Madopar HBS is inadequate. Patients should be carefully observed for possible undesirable psychiatricsymptoms".Deletion of the text "Patients who experience large fluctuations in the medicine's effect in the course of the day (on-off phenomena) should receive more frequent, correspondingly smaller, individual doses, or preferably, the use of Madopar HBS is recommended". Deletion of the text "patients should be informed that their condition may temporarily deteriorate. Patients who experience severe fluctuations during the day (on-off phenomena) should take smaller and more frequent doses. Patients should be carefully monitored for possible psychiatric side effects".Revision of text to read "" under Patients with renal or hepatic impairment	17/01/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Madopar	Levodopa + benserazide	Warnings and Precautions	Revision of text to read "Dopaminergic dysregulation syndrome (DDS): Dopamine dysregulation syndrome (DDS) has been observed in some patients treated with Madopar and is an addictive disorder that leads to excessive use of this or other dopaminergic drugs. Before initiation of treatment, patients and caregivers must be warned of the potential risk of developing DDS (see Undesirable effects)" under Potential for drug dependence or abuse.	17/01/2022	Roche
			Interactions	Addition of the text "However, coadministration of trihexyphenidyl with Madopar HBS does not affect the pharmacokinetics of levodopa" under Pharmacokinetic interactions.		
7	Madopar	Levodopa + benserazide	Undesirable effects	Addition of the text "Rises in blood urea nitrogen (BUN) have been observed with Madopar" under Blood and lymphatic system disorders.Revision of text to read "Frequency not known: dopamine dysregulation syndrome. Dopamine dysregulation syndrome (DDS) is an addictive disorder observed in some patients treated with Madopar. Affected patients show compulsive misuse of dopaminergic drugs, taking higher doses than needed for adequate control of motor symptoms of Parkinson's disease. In some cases this may lead to severe dyskinesia (see Warnings and precautions)" under Psychiatric disorders.	17/01/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
8	Mircera	Methoxy polyethylene glycol-epoetin beta	Dosage/Administration	Revision of text to read "Patients not currently treated with an erythropoiesis-stimulating agent (ESA): Patients not on dialysis – The recommended starting dose is 1.2 µg/kg body weight administered once monthly as a single subcutaneous injection. Alternatively, a starting dose of 0.6 µg/kg bodyweight can may be administered once every two weeks as a single I.V. or S.C injection. Patients on dialysis – The recommended starting dose of 0.6 µg/kg body weight can may be administered once every two weeks as a single IV. or S.C. injection" under Initiation of treatmentRevision of text to read "The MIRCERA dose may be increased by approximately 25% of the previous dose if the rise in hemoglobin is less than 1.0 g/dl (0.621 mmol/l) over a month. Further dose increases of approximately 25% may be made every 4 weeks until the individual target hemoglobin level is achieved.If the rise in hemoglobin exceeds 2 g/dl (1.24 mmol/l) in one month or if the hemoglobin level exceeds 12 g/dl, the dose should be reduced by approximately 25%. If the hemoglobin level continues to increase, therapy should be interrupted until the hemoglobin level begins to decrease, at which point therapy should be restarted at a dose approximately half the previously administered dose. After dose interruption a hemoglobin decrease of approximately 0.35 g/dl (0.22 mmol/l) per week is expected. Dose adjustments should not be made more frequently than once a month. In patients treated once every two weeks whose hemoglobin concentration is above the target range, may receive MIRCERA once monthly at twice the dose previously administered once every two weeks" under Dose adjustment.Deletion of the text "Patients currently treated with an erythropoiesis-stimulating agent (ESA)" under Switching from erythropoiesis stimulating agent (ESA) treatment to Mircera.Revision of text to read "Patients currently treated with an ESA, can be switched to MIRCERA administered once a month as a single intravenous or subcutaneous injection. The starting dose of MIRCERA is calculated from the previous weekly ESA dose at the time of the treatment switch, as described in Table 1. The first MIRCERA injection should be given at the time of the next	17/01/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
				scheduled dose of the previously administered arbepoetin alfa or epoetin." under Switching from erythtopoiesis stimulating agent (ESA) treatment to MirceraRevision of text to read "If a dose adjustment is required to maintain the target hemoglobin concentration above 10 g/dl (6.21mmol/l), the dose may be increased by approximately 25%. If the rise in hemoglobin levels exceeds 2 g/dl (1.24 mmol/l) in one month or if the hemoglobin level exceeds 12 g/dl, the dose should be reduced by approximately 25%. If the hemoglobin level continues to increase, therapy should be interrupted until the hemoglobin level begins to decrease, at which point therapy should be restarted at a dose approximately half the previously administered dose. After dose interruption a haemoglobin decrease of approximately 0.35 g/dl (0.22 mmol/l) per week is expected. Dose adjustments should not be made more frequently than once a month" Table 1 Mircera starting doses.Addition of text "Special dosage instructions; Patients with hepatic impairment;No adjustments of the starting dose or dose modification rules are required in patients with any degree of hepatic impairment (see “Kinetics in specific patient groups”); Elderly patients".Deletion of the text "If a dose of MIRCERA is missed, the missed dose should be administered as soon as possible and treatment with MIRCERA continued at the prescribed dosing frequency; Use in children; Due to limited safety and efficacy data, no dosage recommendations can be given for use in patients under 18 years of age; Use in the elderly; Use in patients with hepatic impairment; No adjustment of the starting dose and no dosage adjustment rule are necessary in patients with hepatic impairment, regardless of its severity (see Pharmacokinetics in special patient populations)".Addition of the text "Children and adolescents; Due to limited safety and efficacy data, no dosage recommendations can be given for use in patients under 18 years of age; Delayed administration; If a dose of Mircera is missed, the missed dose should be administered as soon as possible and treatment with Mircera continued at the prescribed dosing frequency".		

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
8	Mircera	Methoxy polyethylene glycol-epoetin beta	Contraindications	Revision of text to read "Hypersensitivity to the active substance or to any of the excipients listed under “Composition”. MIRCERA must not be used in patients with untreated or poorly controlled hypertension."	17/01/2022	Roche
8	Mircera	Methoxy polyethylene glycol-epoetin beta	Warnings and precautions	Revision of text to read "Hemoglobin target levels above 12 g/dl may be associated with an increased risk of cardiovascular events, including death. Controlled clinical studies have shown no significant benefit attributable to epoetin use when the hemoglobin level is higher than that necessary to controlsymptoms of anemia and avoid blood transfusion".Revision of text to read "Deficiencies of iron, folic acid or vitamin B 12 reduce the effectiveness of ESAs and should therefore be corrected. Intercurrent infections, inflammatory or traumatic episodes, occult blood loss, hemolysis, severe aluminium toxicity, underlying hematological disease or bone marrowfibrosis may also compromise the erythropoietic response. A reticulocyte countshould be considered as part of the evaluation. If all the conditions mentioned are excluded and the patient has a sudden drop of hemoglobin associated with reticulocytopenia and antierythropoietin antibodies, examination of the bone marrow for the diagnosis of pure red cell aplasia [PRCA] should be considered. If PRCA is diagnosed, therapy with Mircera must be discontinued and patients must not be switched to another ESA" under Failure to respond to Mircera therapy should prompt an immediate search for causative factors. Revision of the text to read "Pure red cell aplasia (PRCA)"Revision of text to read "Pure red cell aplasia due to antierythropoietin antibodies has been reported during treatment with ESAs, including MIRCERA. These antibodies cross-react with all ESAs, and patients suspected or confirmed to have antibodies to erythropoietin must not be switched to Mircera" under Pure red cell aplasia (PRCA).Revision of text to read "As with other ESAs, blood pressure may rise during treatment with MIRCERA. Blood pressure	17/01/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
				should be adequately monitored in all patients before, at the initiation of and during treatment with MIRCERA. If high blood pressure is difficult to control by medication or diet, MIRCERA must be reduced in dose or withheld (see Contraindications)" under Blood pressure monitoring.Revision of text to read "The safety and efficacy of MIRCERA therapy have not been investigated in patients with hemoglobinopathies, seizure disorders, bleeding or a recent history of bleeding requiring transfusions or with platelet counts above 500 × 10 9 /l. Caution is therefore required in these patients." under Other.Revision of text to read "In CKD patients the maintenance hemoglobin concentration should not persistently exceed the upper limit of the target hemoglobin concentration recommended under Dosage/Administration. In clinical trials an increased risk of death and serious cardiovascular events wasobserved when erythropoiesis stimulating agents (ESAs) were administered to achieve a target hemoglobin of greater than 12 g/dl (7.5 mmol/l)" under Hemoglobin concentration.Addition of the text "This medicinal product contains less than 1 mmol of sodium (23 mg) per prefilled syringe, i.e. it is virtually “sodium-free”" under Hemoglobin concentration.		
8	Mircera	Methoxy polyethylene glycol-epoetin beta	Interactions	Revision of text to read "No interaction studies have been performed. Clinical studies have produced no evidence that MIRCERA interacts with other medicinal products. The effect of other drugs on the MIRCERA pharmacokinetics and pharmacodynamics was investigated in a population analysis. No evidence was found of an effect on the MIRCERA pharmacokinetics and or pharmacodynamics of MIRCERA"	17/01/2022	Roche

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
8	Mircera	Methoxy polyethylene glycol-epoetin beta	Pregnancy, lactation	Revision of text to read "There are insufficient data on use in pregnant women. Animal studies have shown no direct or indirect toxicity affecting pregnancy,embryonic development, fetal development, parturition (see Preclinicaldata) and/or postnatal development. Caution is required if used during pregnancy" under Pregnancy.Revision of text to read "It is unknown whether methoxy polyethylene glycol-epoetin beta is excreted in human breast milk. One animal study has shown excretion of methoxy polyethylene glycol-epoetin beta in maternal milk. In deciding whether to continue or discontinue breastfeeding during treatment with MIRCERA or to discontinue MIRCERA, the benefit of breastfeeding to the child should be weighed against the benefit of MIRCERA therapy to the woman" under lactation	17/01/2022	Roche

8	Mircera	Methoxy polyethylene glycol-epoetin beta	Undesirable effects	Deletion of text "Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), skin exfoliation and erythema multiforme, have been reported with Mircera in the post-marketing setting (see Warnings and precautions). Frequencies are not known; Clinical trial exposure".Revision of text to read "The MIRCERA safety data from clinical trials are based on 3042 CKD patients, including 1939 patients treated with MIRCERA and 1103 with another ESA. Undesirable effects must be expected in some 6% of patients treated with MIRCERA. The most frequent reported undesirable effect was hypertension (common)". Revision of text to read "Vascular disorders; General disorders andadministration site conditions; Nervous system disorders; Skin and subcutaneous tissue disorders; Immune system disorders" under Organ class - Table 2 Undesirable effects attributed to MIRCERA treatment in controlled clinical trials in CKD patients.Revision of text to read "All other reactions attributed to MIRCERA were rare and in most cases mild to moderate in severity. These reactions could be explained by comorbidities known in the population. In clinical studies, the platelet count decreased slightly during treatment with MIRCERA, but remained within the normal range. Platelet counts below 100 × 10 9 /l were observed in 7.5% of patients treated with MIRCERA and 4.4% of patients treated with ESAs. The safety profile in the paediatric population was consistent with that in adults". Addition of text "Undesirable effects after market launch. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), skin exfoliation and erythema multiforme, have been reported with Mircera in the post-marketing setting (see “Warnings and precautions”). Frequencies are not known".Revision of text to read "The occurrence of neutralizing antierythropoietin antibody-mediated pure red cell aplasia (AEAB-PRCA) has been reported in association with MIRCERA therapy during post-marketing experience (see Warnings and precautions)".Addition of text "Description of selected adverse reactions. Reporting of suspected adverse reactions after marketing authorisation is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reaction".	17/01/2022	Roche

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Safety Updates						
No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
	Mircera	Methoxy polyethylene glycol-epoetin beta	Overdose	Revision of text to read "MIRCERA has a wide therapeutic range. Individual response must be considered when initiating treatment with MIRCERA".Addition of text "Signs and symptoms. Overdose can result in an exaggerated pharmacodynamic effect, e.g. excessive erythropoiesis".Addition of text "Treatment. In case of excessive haemoglobin levels, Mircera should be temporarily withheld (see “Dosage/Administration”). If clinically indicated, phlebotomy may be performed".	17/01/2022	Roche
8			Additional data	Addition of the "Keep out of reach of children" under Special precautions for storage.		
9	Pariet	Rabeprazole sodium	Warnings and Precautions	Addition of texts to read "talk to your doctor or pharmacist before taking pariet if you are due to have a specific blood test (Chromogranin A)."	2/2/2022	Janssen
9	Pariet	Rabeprazole sodium	Pregnancy, breast feeding and fertility	Revision of texts to read "If you are pregnant or breast feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine "	2/2/2022	Janssen
			Possible side effect	Addition of texts to include "Benign polyps in the stomach." Addition of texts to read " Inflammation of the gut (leading to diarrhoea)"		

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Remicade	Infliximab	Possible side effects	Addition of text to read under the sub heading uncommon "Changes in cholesterol and fat levels in the blood"	1/10/202	Janssen
11	Voltaren	Diclofenac Sodium	Warnings and Precautions	Revision of text under the sub heading Gastrointestinal effects "As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Voltaren in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section ADVERSE DRUG REACTIONS). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation and in the elderly. To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of low-dose acetylsalicylic acid (ASA), or other drugs likely to increase gastrointestinal risk.Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors (see section INTERACTIONS). Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see section ADVERSE DRUG REACTIONS).During prolonged	24/01/2022	Novartis

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
				treatment with Voltaren as with other NSAIDs, monitoring of the blood count is recommended. Like other NSAIDs, Diclofenac may temporarily inhibit platelet aggregation. Patient with defects of hemostasis should be carefully monitored"		
12	Zytiga	Abiraterone	Women of child-bearing potential, pregnancy, breast-feeding and fertility	Revision of text under the sub heading Pregnancy "There are insufficient data on the use of diclofenac in pregnant women. Some epidemiological studies suggest an increased risk of miscarriage after use of a prostaglandin synthesis inhibitor (such as NSAIDs) in early pregnancy, however the overall data are inconclusive. Voltaren should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus. Risk of fetal renal impairment with subsequent oligohydramnios has been observed when NSAIDs (including diclofenac) were used from the 20th week of pregnancy onwards.As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus (see sections CONTRAINDICATIONS and NON-CLINICAL SAFETY DATA)."	2/2/2022	Janssen
12	Zytiga	Abiraterone	Special Population	Revision of text under the sub heading Renal impairment " In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of less than 10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile."	2/2/2022	Janssen

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Safety Updates

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
			Posology and method of administration	Revision of texts under method of administration to read "The tablets must be taken as a single dose once daily on an empty stomach. ZYTIGA must be taken at least two hours after eating and food must not be eaten for at least one hour after taking ZYTIGA. ZYTIGA tablets must be swallowed whole with water."		
			Special warnings and precautions for use	Revision of texts under intolerance to excipients to read "This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine. This medicinal product contains 27.2 mg (1.18 mmol) sodium per dose of four tablets, equivalent to 1.36% of the WHO recommended maximum daily intake of 2 g sodium for an adult."		
12	Zytiga	Abiraterone	Pharmacological properties	Revision of texts under pharmacokinetic properties, absorption to read "IZYTIGA tablets must be taken as a single dose once daily on an empty stomach. ZYTIGA must be taken at least two hours after eating and food must not be eaten for at least one hours after taking ZYTIGA. The tablets must be swallowed whole with water (see section 4.2)."	2/2/2022	Janssen
			Preclinical safety data	Addition of subheading to read "Environmental risk assessment (ERA)."		