The underlisted safety variations have been submitted by Marketing Authorization Holders (MAHs) and approved by the Food and Drugs Authority in line with the Variation Guidelines for Allopathic Medicines.These safety variations are being shared with healthcare professionals and patients.

Safety Updates						
No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	Bisoprolol	Bisoprolol	Therapeutic indication	Revision of text to read " Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides (for additional information see section 5.1)".	22-Jan-21	Sandoz
			Posology and method of administration	Revision of text under posology to read "The dosage should be individually adjusted, in particular according to the pulse rate and therapeutic success. It is recommended to start with 5 mg per day. The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg once daily".		
				Addition of text under posology to read "Elderly: It is recommended to start with the lowest possible dose.		
			Posology and method of administration	Revision of text under treatment of stable chronic heart failure to read "Standard treatment of CHF consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocker, diuretics, and when appropriate cardiac glycosides. Patients should be stable (without acute failure) when bisoprolol treatment is initiated. It is recommended that the treating physician be experienced in the management of chronic heart failure. Transient worsening of heart failure, hypotension, or bradycardia may occur during the titration period and thereafter.		
			Special warnings and precautions for use	Revision of texts to read "Bisoprolol must be used with caution in bronchospasm (bronchial asthma, obstructive airways diseases) - diabetes mellitus showing large fluctuations in blood glucose values. Symptoms of hypoglycaemia can be masked - strict fasting - ongoing desensitisation therapy. As with other betablockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment does not always yield the expected therapeutic effect - First degree AV block - Prinzmetal's angina: Cases of coronary vasospasm have been observed. Despite its high beta1-selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal's angina." under this section.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	Bisoprolol	Bisoprolol	Special warnings and precautions for use	Revision of texts to read "General anaesthesia: In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia".	22-Jan-21	Sandoz
				Revision of text to read "Although cardioselective (beta1) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, bisoprolol may be used with caution. In patients with obstructive airways diseases, the treatment with bisoprolol should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnea, exercise intolerance, cough). In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta2-stimulants may have to be increased".		
			Effects on ability to drive and use machines	Revision of text to read "In a study with coronary heart disease patients bisoprolol did not impair driving performance. However, due to individual variations in reactions to the drug, the ability to drive a vehicle or to operate machinery may be impaired. This should be consideredparticularly at start of treatment and upon change of medication as well as in conjunction with alcohol.		
			Undesirable effect	Revision of text under reproductive system and breast disorders from "potency disorders" to "erectile dysfunction"		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Caelyx	Doxorubicin hydrochloride	Possible side effects	Revision of text to read "Like all medicines, this medicine can cause side effects, although not everybody gets them. During the infusion of Caelyx pegylated liposomal, the following reactions may occur: -severe allergic reaction that may include a swollen face, lips, mouth, tongue or throat; difficulty swallowing or breathing; itchy rash (hives) -inflamed and narrowed airways in the lungs, causing coughing, wheezing and shortness of breath (asthma) -flushing, sweating, chills or a fever -chest pain or discomfort -back pain -high or low blood pressure -fast heart beat -fits (seizures) -Leaking of the injection fluid from the veins into the tissues under the skin may occur. If the drip stings or hurts while you are receiving a dose of Caelyx pegylated liposomal, tell your doctor immediately. -Your doctor should be contacted immediately if any of the following serious side effects are noticed: -you develop fever, feel tired, or if you have signs of bruising or bleeding (very common) - redness, swelling and sores, peeling or tenderness, mainly on the palms of your hands andor feet. (‘hand-foot’ syndrome)." under this section.	15-Apr-21	Janssen

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Caelyx	Doxorubicin hydrochloride	Possible side effects	Revision of text to read " These effects have been seen frequently,very commonly and are sometimes severe. In severe cases, these effects may interfere with certain daily activities, and may last for 4 weeks or longer before resolving completely. The doctor may wish to delay the start and/or reduce the dose of the next treatment (see Strategies to prevent and treat hand foot syndrome, below) - pain or sores in mouth or throat, nausea, vomiting, , severe diarrhoea, constipation, loss of appetite, weight loss; or vomiting or nausea (very common) - infections (common), including lung infections (pneumonia) or infections that may affect your vision - being short of breath (common) - severe stomach pain (common) - severe weakness (common) - severe allergic reaction that may include a swollen face, lips, mouth, tongue or throat; difficulty swallowing or breathing; itchy rash (hives) (uncommon) - cardiac arrest (heart stops beating); heart failure, in which the heart does not pump enough blood to the rest of the body, which makes you short of breath and may lead to swollen legs (uncommon) - blood clot that moves to the lungs, causes chest pain and makes you short of breath (uncommon) - swelling, warmth, or tenderness in the soft tissues of your leg, sometimes with pain which gets worse when you stand or walk (rare) severe or life-threatening rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome) or over most of the body (toxic epidermal necrolysis) (rare)" under this section.	15-Apr-21	Janssen

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Caelyx	Doxorubicin hydrochloride	Possible side effects	Revision of text to read "Other side effects Between infusions, the following may occur: Very common side effects (may affect more than 1 in 10 people) -decrease in the number of white blood cells, which can increase the chances of infections. In rare cases, having low white blood cells may lead to severe infection. Anaemia (reduction in red blood cells) may cause tiredness, and decreased platelets in the blood may increase the risk of bleeding. It is because of the potential changes in your blood cells that you will have regular blood tests. -decreased appetite; -constipation; -skin rashes, including redness of the skin, allergic skin rash, red or raised rash on the skin -hair loss -pain including in the muscles and chest muscle, joint, arm, or leg feeling very tired" under Very common side effects.	15-Apr-21	Janssen

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Caelyx	Doxorubicin hydrochloride	Possible side effects	Revision of text to read -"infections, including severe infection throughout the body (sepsis), lung infections, herpes zoster virus infections (shingles), a type of bacterial infection (mycobacterium avium complex infection), urinary tract infection, fungal infections (including thrush and oral thrush in the mouth) infection of the hair roots, infected or irritated throat, infected nose, sinuses or throat (cold) -low number of a type of white blood cell (neutrophils), with a fever -severe weight loss and muscle wasting, not enough water in the body (dehydration), low level of potassium, sodium, or calcium in the blood -feeling confused, feeling anxious, depression, difficulty sleeping -nerve damage that may cause tingling, numbness, pain or loss of pain sensation, nerve pain, unusual feeling in the skin (such as tingling or a crawling feeling), decreased feeling or sensitivity, especially in the skin -change in sense of taste, headache, feeling very sleepy with low energy, feeling dizzy; -inflamed eyes (conjunctivitis) -fast heart beat -high or low blood pressure, flushing -shortness of breath that may be brought on by physical activity, nose bleeds, cough -inflamed stomach lining or foodpipe, ulcers (sores) in the mouth, indigestion, difficulty swallowing, mouth pain, dry mouth -skin problems, including flaky or dry skin, redness of the skin, blister or ulcer (sore) on the skin, itching, dark skin patches -excessive sweating -muscle spasms or aches -pain including in the muscles, bone, or back pain when passing urine -allergic reaction to infusion of the medicine, flu-like illness, chills, inflamed lining of the cavities and passages in the body, such as the nose, mouth or windpipe, feeling weak, generally feeling unwell, swelling caused by fluid build up in the body, swollen hands, ankles or feet -weight loss When Caelyx pegylated liposomal is used alone, some of these effects are less likely to occur, and some have not occurred at all." under Common side effects.		Janssen

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Caelyx	Doxorubicin hydrochloride	Possible side effects	Revision of text to read "-herpes simplex virus infections (cold sores or genital herpes), fungal infection -low number of all types of blood cells, increased number of 'platelets' (cells that help blood to clot) -allergic reaction -high level of potassium in the blood, low level of magnesium in the blood -nerve damage affecting more than one area of the body fits (seizures), fainting -unpleasant or painful sensation, especially to touch, feeling sleepy blurred vision, watery eyes -heart beat feels fast or uneven (palpitations), heart muscle disease, heart damage -tissue damage (necrosis) where the injection is given, inflamed veins that cause swelling and pain, feeling dizzy upon sitting up or standing up -chest discomfort -passing wind, inflamed gums (gingivitis) -skin problems or rashes, including flaky or peeling skin, allergic skin rash, ulcer (sore) or hives on the skin, discoloured skin, change in the natural colour (pigment) of the skin, small red or purple spots caused by bleeding under the skin, nail problems, acne -muscle weakness -breast pain -irritation or pain where the injection is given -swollen face, high body temperature -symptoms (such as inflammation, redness or pain) come back at a part of the body that previously received radiation therapy or was previously damaged by a chemotherapy injection into a vein" under Uncommon side effects.	15-Apr-21	Janssen

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Caelyx	Doxorubicin hydrochloride	Possible side effects	Revision of text to read "-infection that occurs in people with a weak immune system - low number of blood cells made in the bone marrow - inflamed retina, which may cause changes in vision or blindness - abnormal heart rhythm, abnormal heart tracing on an ECG (electrocardiogram) and may be with a slow heart beat, problem with the heart that affects the heart beat and rhythm, blue colour to the skin and mucosa caused by low oxygen in the; - widening of blood vessels - tight feeling in the throat - sore and swollen tongue, ulcer (sore) on the lip - skin rash with fluid-filled blisters - vaginal infection, redness of the scrotum - problems with the lining of the cavities and passages in the body, such as the nose, mouth or windpipe - abnormal liver blood test results, increased level of 'creatinine' in the blood" under Rare side effects.	15-Apr-21	Janssen
				Addition of text "Not known (frequency cannot be estimated from the available data) - cancer of the blood that develops quickly and affects the blood cells (acute myeloid leukaemia), bone marrow disease that affects the blood cells (myelodysplastic syndrome), cancer of the mouth or lip" under this section		
3	Dostinex	Cabergoline	Warnings and precaution	Revision of text to read "If you have just given birth, you may be at risk of developing certain conditions. These may include hypertension, infarction, seizures, stroke or psychiatric disorders. Your doctor will, therefore, have to monitor your blood pressure regularly during the treatment. Contact your doctor immediately if you develop hypertension, chest pain or unusually severe or persistent headache (with or without sight problems)". under this section.	13-Jan-21	Pfizer
			Possible side effects	Revision of text from hair loss to "partial balding" under this section.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Enbrel	Etanercept	Qualitative and Quantitative Composition	Addition of sub-heading "Solution for injection in pre-filled syringe" under Physical Characteristics	24-Feb-21	Pfizer
			Posology and methof of administration	Addition of text to read "Missed doses - If a dose is missed, patients should be advised to administer the dose as soon as they remember, unless the next scheduled dose is the next day, in which case the missed dose should be skipped. Patients should continue to inject the medicine on their usual day(s). If a patient does not remember until the day that the next injection is due, instruct the patient not to take a double dose" under Method of Administration. Revision of text to read "Enbrel has not been studied in children <2 years of age (see section 4.1). For pediatric specific safety information concerning malignancies, and vaccinations, see sections 4.4 and 4.8" under Paediatric Use.		
			Special warnings and precautions for use	Addition of text to read "Solution for injection in pre filled syringe-The needle cover of the pre-filled syringe and the needle cap of the pre-filled pen contain latex (dry natural rubber). Patients or caregivers should contact their doctor before using Enbrel if the needle cover will be handled by or if Enbrel will be given to someone with a known or possible hypersensitivity (allergy) to latex."under the sub-heading Allergic reactions.		
5	Mabthera 1400mg SC	Rituximab	Qualitative and quantitative Composition	Revision of text to read" Each ml contains 120 mg of rituximab. Each vial contains 1400 mg/11.7 ml rituximab. Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures. For the full list of excipients, see section 6.1. under this section.	15-Jan-21	Roche
			Pharmaceutical form	Revision of text to read " Solution for injection. Clear to opalescent, colorless to yellowish liquid with pH of 5.2 – 5.8 and osmolality of 300 - 400 mOsmol/kg. " under this section.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Mabthera 1400mg SC	Rituximab	Therapeutic indication	Revision of text to read " MabThera is indicated in adults for nonNon-Hodgkin's lymphoma (NHL). MabThera is indicated for the treatment of previously untreated patients with stage 3-4III - IV follicular lymphoma in combination with chemotherapy. " under this section.	15-Jan-21	Roche
			Posology and method of administration	Revision of text to read " MabThera subcutaneous formulation is not intended for intravenous administration and should be given via subcutaneous injection only. The 1400 mg strength is intended for subcutaneous use in non Hodgkin lymphoma (NHL) only." under sub-heading Posology.		
			Special warnings and precautions for use	Revision of text to read " In order to improve traceability of biological medicinal products, the tradename and batch number of the administered product should be clearly recorded." under sub-heading Traceability.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Mabthera 1400mg SC	Rituximab	Undesirable effects	Revision of text to read "The overall safety profile of MabThera in non Hodgkin's lymphoma and chronic lymphocytic leukemia (CLL) is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with MabThera monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy. The most frequently observed adverse reactions (ADRs) in patients receiving MabThera were infusion-related reactions which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1% after eight doses of MabThera. □ Infectious events (predominantly bacterial and viral) occurred in approximately 30 55% of patients during clinical trials in patients with NHL and in 30-50% of patients during clinical trial in patients with CLL. The most frequent reported or observed serious adverse reactions were: •□nfusion-related reactions (including cytokine release syndrome, tumor lysis syndrome), see section 4.4. •□nfections, see section 4.4. •□ardiovascular disorders, see section 4.4. Other serious ADRs reported include hepatitis B reactivation and PML (see section 4.4). The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarized in Table 1. Frequencies are defined as very common (□ 1/10), common (□ 1/100 to < 1/10), uncommon (□ 1/1000 to < 1/100), rare (□ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "not known"." under the sub heading Experience from non-Hodgkin's lymphoma and chronic lymphocytic leukemia.	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Mabthera 1400mg SC	Rituximab	Pharmacodynamic properties	Revision of text to read "Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, ATC code: L01X C02 MabThera subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered substances when administered subcutaneously." under this section. Revision of text to read " Data from the development programme of MabThera subcutaneous formulation indicate that the formation of anti-rituximab antibodies after subcutaneous administration is comparable with that observed after intravenous administration. In the SABRINA trial (BO22334), the incidence of treatment-induced/-enhanced anti-rituximab antibodies was low and similar in the intravenous and subcutaneous groups (1.9% vs. 2%, respectively). The incidence of treatment-induced/-enhanced anti-rHuPH20 (-recombinant human hyaluronidase) antibodies was 8% in the intravenous group compared with 15% in the subcutaneous group, and none of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies. " under Immunogenicity.	15-Jan-21	Roche
			Shelf life	Revision of text to read "After first opening Once transferred from the vial into the syringe, the solution of MabThera subcutaneous formulation is physically and chemically stable for 48 hours at 2 °C 8 °C and subsequently for 8 hours at 30 °C in diffuse daylight. From a microbiological point of view, the product should be used immediately. If not used immediately, preparation should take place in controlled and validated aseptic conditions. In-use storage times and conditions prior to use are the responsibility of the user." under this section.		
			Nature and contents of container	Deletion of text " Colorless type I glass vial with butyl rubber stopper with aluminium over seal and a pink plastic flip-off disk, containing 1400 mg/11.7 ml of rituximab. Each carton contains one vial." under the entire section		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	Mabthera 1600mg SC	Rituximab	Qualitative and quantitative Composition	Deletion of text "Excipients with known effects: This medicinal product contains less than 1 mmol sodium per dose, i.e. essentially sodium free." under this section.	15-Jan-21	Roche
			Pharmaceutical form	Revision of text to read "Solution for injection. Clear to opalescent, colourless to yellowish liquid with pH of 5.2 – 5.8 and osmolality of 300 - 400 mOsmol/kg. " under this section.		
			Special warnings and precautions for use	Revision of text to read " In order to improve traceability of biological medicinal products, the tradename and batch number of the administered product should be clearly recorded." under Traceability		
			Interaction with other medicinal products and other forms of interaction	Revision of text to read " Patients with human anti-mouse antibody (HAMA) or anti-drug antibody (ADA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies." under this section.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	Mabthera 1600mg SC	Rituximab	Undesirable effects	Revision of text to read "The overall safety profile of MabThera in non Hodgkin's lymphoma and chronic lymphocytic leukemia (CLL) is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with MabThera monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy. The most frequently observed adverse reactions (ADRs) in patients receiving MabThera were infusion-related reactions which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1% after eight doses of MabThera. Infectious events (predominantly bacterial and viral) occurred in approximately 30 55% of patients during clinical trials in patients with NHL and in 30-50% of patients during clinical trial in patients with CLL. The most frequent reported or observed serious adverse reactions were: •Infusion-related reactions (including cytokine release syndrome, tumor lysis syndrome), see section 4.4. •Infections, see section 4.4. •Cardiovascular disorders, see section 4.4. Other serious ADRs reported include hepatitis B reactivation and PML (see section 4.4). The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarized in Table 1. Frequencies are defined as very common (1/10), common (1/100 to < 1/10), uncommon (1/1000 to < 1/100), rare (1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "not known"." under the sub heading Experience from non-Hodgkin's lymphoma and chronic lymphocytic leukemia.	15 Jan 2021	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	Mabthera 1600mg SC	Rituximab	Pharmacodynamic properties	Revision of text to read" A two-part phase Ib, multicenter, randomised, open-label, parallel-group trial (SAWYER BO25341) was conducted in patients with previously untreated CLL, to investigate the non-inferiority of the pharmacokinetic profile, together with efficacy and safety of MabThera subcutaneous formulation in combination with chemotherapy. The objective of the Part 1 was to select a MabThera subcutaneous formulation dose that resulted in comparable MabThera serum Ctrough levels compared with MabThera intravenous formulation. A number total of 64 patients with CLL were enrolled at any point prior to cycle 5 during their treatment with MabThera intravenous formulation in combination with chemotherapy. The dose of 1600 mg of MabThera subcutaneous formulation was selected for the Part 2 of the study. The objective of the Part 2 was to establish the non-inferiority in observed Ctrough levels between the confirmed selected MabThera subcutaneous dose and the reference MabThera intravenous dose. A number total of 176 patients with CLL were randomised into the following two treatment groups: •MabThera subcutaneous (n=88); 1st cycle of MabThera intravenous 375 mg/m2 in combination with chemotherapy plus subsequent cycles (2–6) of MabThera subcutaneous 1600 mg in combination with chemotherapy. •MabThera intravenous (n=88): 1st cycle of MabThera intravenous 375 mg/m2 in combination with chemotherapy followed by up to 5 cycles of MabThera intravenous 500 mg/m2 in combination with chemotherapy. The response rates for the analysis of 176 patients in SAWYER Part 2 are shown in Table 2. Overall the results confirm that MabThera subcutaneous formulation 1600 mg has a comparable benefit/risk profile to that of MabThera intravenous formulation 500 mg/m2." under this section. Revision of table titled " Table 2:Efficacy results for SAWYER (BO25341) (Intent to Treat Population)" under this section.	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	Mabthera 1600mg SC	Rituximab	Pharmacodynamic properties	Revision of text to read "Data from the development programme of MabThera subcutaneous formulation indicate that the formation of anti-rituximab antibodies after subcutaneous administration is comparable with that observed after intravenous administration. In SAWYER trial (BO25341) the incidence of treatment-induced/enhanced anti-rituximab antibodies was similar in the two treatment arms; 15% intravenous vs. 12% subcutaneous. The incidence of treatment-induced/enhanced anti-rHuPH20 antibodies, only measured in patients in the subcutaneous arm was 12%. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralising antibodies. The clinical relevance of the development of anti-rituximab or anti-rHuPH20 antibodies after treatment with MabThera subcutaneous formulation is not known. There was no impact of the presence of anti-rituximab or anti-rHuPH20 antibodies on safety, efficacy or PK of MabThera." under the sub-heading Immunogenicity.	15-Jan-21	Roche
			Shelf life	Revision of text to read "After first opening Once transferred from the vial into the syringe, the solution of MabThera subcutaneous formulation is physically and chemically stable for 48 hours at 2 °C 8 °C and subsequently for 8 hours at 30 °C in diffuse daylight. From a microbiological point of view, the product should be used immediately. If not used immediately, preparation should take place in controlled and validated aseptic conditions. In-use storage times and conditions prior to use are the responsibility of the user." under this section.		
			Nature and contents of container	Deletion of text " Colorless type I glass vial with butyl rubber stopper with aluminium over seal and a pink plastic flip-off disk, containing 1400 mg/11.7 ml of rituximab. Each carton contains one vial." under the entire section		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Composition	Revision of text to "Rituximab (produced by recombinant DNA technology using CHO [Chinese hamster ovary] cells). Excipients: Polysorbate 80 (produced from genetically modified maize), sodium chloride, sodium citrate, sodium hydroxide, hydrochloric acid, water for injection. Each 10 ml vial of concentrate contains 52.6 mg of sodium; each 50 ml vial of concentrate contains 263 mg of sodium." under this section.	15-Jan-21	Roche
			Pharmaceutical form and active substance quantity per unit	Revision of text to read "1 rubber-stoppered vial with 10 ml concentrate for solution for infusion contains 100 mg rituximab. 1 rubber-stoppered vial with 50 ml concentrate for solution for infusion contains 500 mg rituximab." under this section.		
			Dosage/Administration	Revision of text to read "MabThera infusions should be administered in a medical facility in which the resources for effective resuscitation can be immediately deployed. The infusions should be administered under the direct supervision of a physician experienced in the respective specialty. MabThera can be administered in an outpatient setting. Patients who develop respiratory symptoms or hypotension should be monitored for at least 24 hours. MabThera is administered after dilution as an i.v. infusion through a dedicated line. MabThera must not be injected i.v. undiluted, nor may the prepared solution for infusion be administered as a bolus infusion." under this section. Addition of headings "Initiation of treatment and Dose adjustment following undesirable effects/interactions" under this section. Revision of text to read "In untreated patients, MabThera is administered every 2 months (375 mg/m2 body surface area) until disease progression or up to a maximum duration of two years (12 infusions in total). In relapsed or refractory patients who have responded to induction therapy, MabThera is administered every 3 months (375 mg/m2 body surface area) until disease progression or up to a maximum duration of two years (8 infusions in total)." under the heading Maintenance therapy.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Dosage/Administration	Revision of text to read " It is recommended that 48 hours before the start of treatment prophylaxis with adequate fluid intake and administration of urostatic agents be initiated in order to reduce the risk of tumour lysis syndrome. In addition, consideration should be given to premedication with glucocorticoids shortly before the start of the infusion with MabThera in order to reduce the frequency and severity of acute infusion-related reactions (IRRs) and/or of cytokine release syndrome. The recommended dose of MabThera in previously untreated or relapsed/refractory CLL patients is 375 mg/m2 body surface area on day 1 of the first treatment cycle, followed by 500 mg/m2 body surface area on day 1 of cycles 2–6 (at four-week intervals). Fludarabine 25 mg/m2 and cyclophosphamide 250 mg/m2 are given on days 2, 3 and 4 in the first cycle and days 1–3 in cycles 2–6. The following dosage adjustments are recommended if severe infections occur or if grade 3 or 4 cytopenia (anaemia, neutropenia, thrombocytopenia) that is not indicative of bone marrow involvement occurs on day 28 of a cycle: Treatment can be postponed for 2 weeks and the dose of fludarabine and cyclo-phosphamide can be reduced by 25% in the following cycles. In the event that after this first dose reduction a second episode of grade 3 or 4 cytopenia occurs on day 28 of a cycle independently of bone marrow involvement, treatment can once again be postponed by up to 2 weeks and the dose of fludarabine and cyclophosphamide reduced by a further 25%. This results in a dose equivalent to 50% of the normal fludarabine/cyclophosphamide dose." under the heading Chronic lymphocytic leukaemia (CLL).	15-Jan-21	Roche
				Revision of text to read " Premedication with glucocorticoids should also be administered to decrease the frequency incidence and severity of IRRs. Patients should receive 100 mg i.v. methylprednisolone i.v. to be completed 30 minutes prior to each MabThera infusion (see Warnings and precautions)." under the heading Rheumatoid arthritis. Revision of text to read "Children and adolescents The use and safety of MabThera in children and adolescents have not yet been investigated. Elderly patients No dose adjustment is required in elderly patients (>65 years of age). Patients with hepatic or renal impairment No experience is available in patients with hepatic or renal impairment." under the heading Special dosage instructions.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Contraindications	Revision of text to read " Hypersensitivity to the active substance or to any of the excipients listed under “Composition”. Patients with severe heart failure (NYHA class IV). The combination of rituximab with chemotherapeutic agents including methotrexate is during pregnancy and lactation." under this section.	15-Jan-21	Roche
			Warnings and precautions	Revision of text to read " Progressive multifocal leukoencephalopathy- Cases of progressive multifocal leukoencephalopathy (PML) have been reported during or after the use of MabThera. Two cases of fatal PML in NHL patients were also observed in a clinical phase III study after disease progression and retreatment. The majority of patients had received MabThera in combination with chemotherapy or in a context of haematopoietic stem cell transplantation. In the differential diagnosis of patients developing neurological symptoms the possibility of PML must be considered. Patients must be monitored at regular intervals for emergent or worsening symptoms indicative of PML. PML is frequently fatal and resistant to all therapy. PML signs and symptoms are varied, progress over days to weeks and may comprise increasing weakness in one side of the body or clumsiness in the limbs, loss of balance, visual disturbances and impairment of cognition, memory and orientation, leading to confusion and personality changes. If in doubt, further investigations should be considered, including MRI (preferably contrast-enhanced), testing of the cerebrospinal fluid for JC virus DNA and serial neurological assessment. The physician should be alert to signs and symptoms indicative of PML, in particular those unnoticed by the patient (e.g. cognitive, neurological or psychiatric signs). The patient should in addition be advised to inform their partner or carers about their treatment since these persons may observe signs that escape the patient’s notice. If PML is suspected, prompt neurological workup is indicated and treatment should be suspended until PML is excluded. If PML is confirmed, MabThera must be permanently withdrawn. Following reconstitution of the immune system, stabilisation or improvement has been observed in immunosuppressed patients with PML. It is not known whether early detection of PML and suspension of MabThera treatment could lead to similar stabilisation or improvement."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Warnings and precautions	Revision of text to read "Treatment with MabThera, especially administration of the first dose, may be associated with infusion reactions (IRRs) related to the release of cytokines and/or other chemical mediators. The incidence of IRRs decreased from 77% (7% grade 3 and 4) with the first infusion to approximately 30% (2% grade 3 and 4) with the fourth infusion and to 14% (no grade 3 or 4 events) with the eighth infusion. In general, the proportion of patients experiencing an IRR was higher after the first infusion of a cycle than after the second infusion. Subsequent MabThera cycles were better tolerated by patients than the first cycle. Signs and symptoms that indicate an IRR are itch, fever, urticaria/rash, chills, pyrexia, sneezing, angioneurotic oedema, throat irritation, cough and bronchospasm – with or without associated hypotension or hypertension. The reported reactions were generally reversible when the infusion of MabThera was administered more slowly or interrupted and an antipyretic, an antihistamine and – in isolated cases and if required – oxygen, i.v. saline solution or bronchodilators and glucocorticoids were administered. It is recommended that IRRs be treated with diphenhydramine and paracetamol/acetaminophen. Additional treatment with bronchodilators or intravenous saline solution may be indicated. Depending on the severity of the IRRs and measures interventions, MabThera may have to be temporarily or permanently withdrawn. In most cases the infusion can be continued with a 50% reduction of infusion rate (e.g. from 100 mg/hour to 50 mg/hour) after complete resolution of signs and symptoms. Most patients other than those with life-threatening IRRs were able to complete the treatment cycle with MabThera. Only rarely have severe IRRs recurred during subsequent treatment of patients whose signs and symptoms have resolved completely." under the heading Infusion-related reactions.	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Warnings and precautions	Revision of text to read " Severe IRRs may be clinically indistinguishable from hypersensitivity reactions or cytokine release syndrome. Severe IRRs with fatal outcome have been reported. Severe IRRs, which are characterised by pulmonary events, generally commence within 30 minutes to two hours after the start of the first MabThera infusion and in some cases have also included rapid tumour lysis and signs of tumour lysis syndrome as well as fever, chills, rigors, hypotension, urticaria, angioedema and other signs and symptoms (see “Undesirable effects”). Premedication consisting of an analgesic/antipyretic and an antihistamine should always be administered before each MabThera infusion. Premedication with glucocorticoids should also be administered to RA and CLL patients to decrease the incidence and severity of IRRs (see “Dosage/Administration”). Higher doses of intravenous glucocorticoids were administered in patients with ANCA-associated vasculitis., In RA patients most of the IRRs reported in clinical studies were mild to moderate in severity. In clinical studies a severe infusion reaction occurred, independently of dose, in 14 of 3095 patients (<1%) with rheumatoid arthritis who received a first infusion of MabThera. In post-marketing experience in RA, four severe IRRs have been reported with fatal outcome (in a total of approximately 150,000 treated RA patients). Patients with pre-existing heart disease and those with a history of previous unwanted cardiopulmonary effects should be closely monitored. Infusion-related reactions in ANCA-associated vasculitis patients were comparable to those observed in RA patients." under the heading Infusion-related reactions	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Warnings and precautions	Revision of text to read " The occurrence of anaphylactic and other hypersensitivity reactions has been reported after intravenous administration of proteins to patients. Adrenaline, antihistamines and glucocorticoids should be available for immediate use in the event of a hypersensitivity reaction to MabThera." under the heading Hypersensitivity reactions/anaphylaxis. Revision of text to read "Pulmonary events including hypoxia, pulmonary infiltrates and acute respiratory failure have occurred. Some of these events were preceded by severe bronchospasm and dyspnoea. In some cases the signs and symptoms worsened over time, while in other cases an initial improvement was followed by a clinical deterioration. Patients with pulmonary events or other severe IRRs must therefore be closely monitored until their signs and symptoms have resolved completely. Patients with a history of respiratory failure or with pulmonary tumour infiltration are at greater risk of an unfavourable outcome and should therefore be treated with greater caution. Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome generally appears within one to two hours after the start of the first infusion. In patients with severe pulmonary events the infusion must be stopped immediately and symptomatic therapy initiated." under the heading Pulmonary events. Revision of text to read " Since transient hypotension may occur during MabThera infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout MabThera infusion. Cases of MabThera administration were observed in which pre-existing ischaemic heart disease became manifest and caused symptoms such as angina pectoris, myocardial infarction, atrial fibrillation and atrial flutter Therefore, in patients with a history of heart disease, the risk for of cardiovascular compli-cations due to IRRs should be considered prior to treatment with MabThera. Patients with a history of heart disease (e.g. angina pectoris, cardiac arrhythmias such as atrial flutter or fibrillation, heart failure or myocardial infarction) should be closely monitored during the infusion. No data are available on the safety of MabThera in patients with moderately severe heart failure (NYHA class III). Patients with severe heart failure (NYHA class IV) should not be treated." under the heading Cardiovascular system/heart failure.	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Warnings and precautions	Revision of text to read " Caution should be exercised when treating patients with neutrophil counts of <1.5 × 109/l and/or platelet counts of <75 × 109/l, as clinical experience with such patients is limited. As with other tumour therapies, regular monitoring of full blood count, including platelet count, is indicated." under the heading Monitoring of blood counts. Revision of text to read " The physician should review vaccination status and follow local/national immunisation guidelines for adults against infectious diseases prior to treatment with MabThera. If possible, patients should receive any outstanding vaccinations in accordance with current immunisation guidelines before starting treatment with MabThera. The vaccinations should be completed at least four weeks prior to first administration of MabThera. The safety of immunisation with vaccines, especially live vaccines, following MabThera therapy has not been studied, nor whether a primary humoral response to vaccines is possible. Patients treated with MabThera must not receive live viral vaccines. If necessary, they may be immunised with non-live vaccines. Response to inactivated vaccines may be reduced during and after treatment with MabThera. In a non-randomised study, patients receiving MabThera monotherapy had a lower response rate (when assessed for a >2-fold increase in antibody titre) to testing with tetanus recall antigen (16% vs 81%) and keyhole limpet haemocyanin (KLH) (4% vs 76%), compared to untreated controls. Mean pre-therapeutic antibody titres against a panel of antigens (Streptococcus pneumoniae, influenza A, mumps, rubella, varicella) were maintained for at least 6 months after treatment with MabThera. Patients treated with either MabThera and methotrexate or methotrexate alone showed similar response rates to tetanus recall antigen (39% vs 42%) and decreased response rates to pneumococcal polysaccharide vaccine (43% vs 82%) 6 months after completing MabThera treatment. In repeat treatment over one year the proportions of patients with positive antibody titres against S. pneumoniae, influenza, mumps, rubella, varicella and tetanus toxoid were generally similar to the proportions at baseline." under the heading Preventive vaccinations.	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Warnings and precautions	Revision of text to read " Severe mucocutaneous reactions, some with fatal outcome, have been reported in isolated patients treated with MabThera. These reactions occurred between 1 and 13 weeks after the start of treatment. Affected patients must receive no further infusions and undergo a medical examination immediately. A skin biopsy is useful for distinguishing between different skin reactions and determining subsequent treatment. The mucocutaneous reactions reported included paraneoplastic pemphigus, lichenoid dermatitis and vesiculobullous dermatitis. Nothing is known regarding the safety of retreatment with MabThera in these cases. Severe skin reactions, such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some of which were fatal, have been reported (see “Undesirable effects”). In such an event, with a suspected relationship to MabThera, treatment should be permanently discontinued. " under the heading Skin reactions. Revision of text to read " The risk of infection is potentially increased after treatment with MabThera. MabThera should not be administered to patients with active infection or severely impaired immune response (e.g. hypogammaglobulinaemia, severely reduced CD4 or CD8 cell counts). Caution is required when MabThera is prescribed for patients with a history of recurrent or chronic infection or an underlying disease that favours the occurrence of severe infections (see “Undesirable effects”). Patients who develop an infection after treatment with MabThera should be promptly investigated and appropriately treated." under the heading Infections. Revision of text to read " Patients with severe viral infections should not be treated with MabThera. Severe viral infections, both new and reactivated or exacerbated, have been reported on treatment with rituximab and have been fatal in isolated cases. The majority of patients had received rituximab in combination with chemotherapy or in the context of haematopoietic stem cell transplantation. Examples of such severe viral infections include infections with herpesviruses (cytomegalovirus, varicella zoster virus, herpes simplex virus), JC virus (progressive multifocal leukoencephalopathy [PML]) and hepatitis B and C viruses." under the heading Severe viral infections .	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Warnings and precautions	Revision of text to read " Cases of hepatitis B reactivation – including fulminant hepatitis, sometimes with fatal outcome – have been reported; the majority of affected patients were also receiving cytotoxic chemotherapy. Causality cannot be clearly distinguished. Hepatitis B virus (HBV) screening according to local guidelines should be performed in all patients before initiation of treatment with MabThera. At minimum this should include determination of HBsAg and anti-HBc, and should be complemented with other appropriate markers. Patients with active hepatitis B should not be treated with MabThera. Patients with positive hepatitis B serology should consult a liver disease specialist before the start of treatment and should be monitored and managed according to usual local standard medical practice to prevent hepatitis B reactivation." under the heading Hepatitis B infection. Revision of text to read " Gastrointestinal perforation or obstruction, in a few cases leading to death, has been observed in patients who received rituximab in combination with chemotherapy for the treatment of non-Hodgkin's lymphoma. Complaints of abdominal pain, especially at the start of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment. " under the heading Gastrointestinal tract . Revision of text to read " There have been post-marketing reports of cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS). Signs and symptoms included visual disturbances, headaches, seizures and altered mental state with or without associated hypertension. The diagnosis of PRES/RPLS must be confirmed by brain imaging. In the reported cases there were recognised risk factors for PRES/RPLS including patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy. " under the heading Nervous system disorders.	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Warnings and precautions	Revision of text to read " Tumour lysis syndrome-MabThera brings about rapid lysis of benign and malignant CD20-positive cells and can precipitate tumour lysis syndrome with hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, elevated LDH levels and acute renal failure. Patients with a high number [>25,000/mm3] of circulating malignant cells or a high tumour burden (lesions >10 cm) are at higher risk of tumour lysis syndrome and should be treated with extreme caution. In patients at risk for the development of tumour lysis syndrome the need for appropriate prophylaxis should be considered. In these patients the infusion rate should be reduced or infusion spread over two days in the first cycle, and in all subsequent cycles if the lymphocyte count remains above 25,000/mm3. The patients should be monitored particularly closely during administration of the first infusion." under the heading Patients with haematological malignancies. Revision of text to read " The efficacy and safety of MabThera for the treatment of autoimmune diseases other than rheumatoid arthritis and ANCA-associated vasculitis have not been studied. An electrocardiogram should be performed before starting treatment of ANCA-associated vasculitis." under the heading Patients with rheumatoid arthritis & ANCA-associated vasculitis. Revision of text to read " The efficacy and safety of MabThera in the treatment of autoimmune diseases other than rheumatoid arthritis have not been studied. No data are available for patients with severe pulmonary disease. Caution should therefore be exercised when MabThera is used in these patients. No data are available for patients with anaemia (Hb <8.5 g/dl) or neutropenia (neutrophil count <1500/µl). This medicinal product contains 52.6 mg of sodium per 10 ml vial and 263.2 mg of sodium per 50 ml vial, corresponding to 2.63% and 13.16%, respectively, of the WHO-recommended maximum daily dietary sodium intake of 2 g for an adult." under the heading Further warnings and precautions.	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Pregnancy , Lactation	Revision of text to read "IgG immunoglobulins are known to cross the placental barrier. Because of the long retention time of MabThera in patients with B-cell depletion, women of childbearing age in whom treatment is unavoidable and cannot be deferred should use a reliable method of contraception during treatment with MabThera and for 12 months thereafter. No fetal damage was found in reproductive toxicology studies in monkeys. B cell-depleted populations were found in the postnatal phase in neonatal offspring of dams that had been exposed to MabThera during pregnancy. No studies of B-cell populations in human neonates after maternal exposure to MabThera have been performed. There are no adequate and well-controlled data on use in pregnant women, but transient B-cell depletion and lymphocytopenia have been observed in some infants born to mothers exposed to rituximab during pregnancy. For these reasons MabThera must not be administered to pregnant women unless clearly necessary." under the heading Pregnancy	15-Jan-21	Roche
			Effects on ability to drive and use machines	Revision of text to read " No relevant studies have been performed on the effects of MabThera on the ability to drive and use machines. The pharmacological action and the undesirable effects observed to date do not suggest the likelihood of any such effects. Nevertheless, the influence of premedication with antihistamines should be noted. After IRRs the patient's condition should be allowed to stabilise before the patient drives vehicles or operates machines." under theis section.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Undesireable effects	Addition of "decreased IgG levels" with frequency Very common under the System Organ Class Immune system disorders under the sub-heading Experience from clinical studies in NHL. Revision of text to read " Isolated cases: peripheral neuropathy, sensory disturbances, facial nerve palsy." under the System Organ Class Nervous system disorders under the sub-heading Experience from clinical studies in NHL. Deletion of text "Very common: decreased IgG levels." under Investigations from the sub-heading Experience from clinical studies in NHL. Reviosion of text to read "The safety and efficacy of MabThera have not been studied in paediatric patients. Hypogammaglobulinaemia has been observed in paediatric patients treated with MabThera; some cases were severe, requiring long-term immunoglobulin replacement therapy. The consequences of long-term B-lymphocyte deficiency in paediatric patients are unknown." under the sub-heading Experience from clinical studies in rheumatoid arthritis and & ANCA-associated vasculitis. Deletion of text " Very rare: severe IRRs with fatal outcome have been reported in the postmarketing experience. Hypogammaglobulinemia (IgM, IgG or IgA below the normal range) has been observed in RA patients and in ANCA-associated vasculitis." ubder Immune system disorders from the sub-heading Experience from clinical studies in rheumatoid arthritis and & ANCA-associated vasculitis. Deletion of text "Isolated cases of toxic-epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), some of which were fatal, have been reported in the postmarketing setting." under Skin and subcutaneous tissue disorders from the sub-heading Experience from clinical studies in rheumatoid arthritis and & ANCA-associated vasculitis..	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Undesireable effects	Addition of text "Immune system disorders Very rare: severe IRRs with fatal outcome have been reported in post-marketing experience. Hypogammaglobulinaemia (IgM, IgG or IgA below the normal range) has been observed in RA patients and in ANCA-associated vasculitis. Skin and subcutaneous tissue disorders Isolated cases of toxic-epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), some of which were fatal, have been reported in post-marketing experience. Nervous system disorders There have been post-marketing reports of cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS). Symptoms include visual disturbances, headache, seizures and altered mental state, with or without associated hypertension. The diagnosis of PRES/RPLS must be confirmed by brain imaging. In the reported cases there were recognised risk factors for PRES/RPLS, including hypertension, immunosuppressive therapy and/or other concomitant treatments. 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." under Undesirable effects after market launch of the sub-heading Experience from clinical studies in rheumatoid arthritis and & ANCA-associated vasculitis.	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Overdose	Revision of text to read "No cases of overdose have been reported. No experience with overdosage is available from clinical trials in humans. Single doses higher than 1000 mg have not been evaluated in controlled clinical studies. The highest dose tested to date in patients with chronic lymphatic leukaemia was 5 g. Treatment- In the event of overdosage the infusion should be stopped immediately and the patient closely monitored. In patients with B-cell depletion the blood count should be checked regularly and attention paid to the increased risk of infection." under this section.	15-Jan-21	Roche
			Properties/Effects	Revision of text to read "Combination with CVP In a randomised open study a total of 321 previously untreated patients with low-grade or follicular B cell non-Hodgkin's lymphoma received CVP chemotherapy (cyclophosphamide 750 mg/m2 body surface area vincristine 1.4 mg/m2 body surface area up to a maximum of 2 mg on day 1 and prednisolone 40 mg/m2 body surface area/day on days 1–5) every 3 weeks for 8 treatment cycles or MabThera 375 mg/m2 body surface area in combination with CVP (R CVP). MabThera was administered on day 1 of each treatment cycle. R CVP led to significant benefit over CVP in terms of the primary endpoint (time to "treatment failure", defined as progression, relapse after response, institution of new lymphoma therapy, no response after 4 cycles, death: 25.9 months versus 6.7 months, p<0.0001)." under the sub-heading Clinical efficacy- Follicular Non-Hodgkin's lymphoma.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Pharmacokinetics	Revision of text to read "Absorption- Not applicable Distribution-The mean Cmax following the fourth infusion of 375 mg/m2 was 486 µg/ml (range 77.5 to 996.6 µg/ml). Following the intravenous administration of 500 and 1000 mg doses of MabThera on two occasions two weeks apart, mean Cmax values were 183 µg/ml (range 81.8 to 279 µg/ml) and 370 µg/ml (range 212 to 637 µg/ml) respectively. The mean steady-state distribution volume was approximately 4.6 l (range 1.7 to 7.51 l). Metabolism Like all proteins, rituximab is broken down in the liver. Elimination The estimated mean terminal elimination half-life of rituximab is 20.8 to 24 days (range 6.1 to 52 days). Tumour mass has an influence on specific clearance. Kinetics in specific patient groups Age, sex, ethnicity and WHO performance status had no influence on the pharmacokinetics of rituximab. Hepatic/renal impairment No pharmacokinetic data are available in patients with hepatic or renal impairment." under this section.	15-Jan-21	Roche
			Preclinical data	Safety pharmacology There have been no preclinical studies of the combination of MabThera and methotrexate. Mutagenicity/carcinogenicity Mutagenicity and carcinogenicity of MabThera have not been studied. Reproductive toxicity Developmental toxicity studies of rituximab performed in cynomolgus monkeys at doses up to 100 mg/kg body weight (from days 20 to 50 of gestation) revealed no evidence of rituximab-induced fetotoxicity. However, pharmacological dose-dependent B-cell depletion was observed in the fetal lymphoid tissue. This persisted after birth and was associated with decreased IgG concentrations in the newborns concerned. B-cell counts reverted to normal in these animals within six months after birth and did not impair the response to immunisation." under this section.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Mabthera 1500mg IV	Rituximab	Other information	Revision of text to read "Incompatibilities-No incompatibilities between MabThera and polyvinylchloride or polyethylene bags or infusion sets have been observed. MabThera may be mixed only with those medicinal products listed under Instructions for handling . Effects on diagnostic methods- Possible effects on response to vaccines and on diagnostic tests based on the demonstration of antibodies have not been investigated. Shelf life- Do not use this medicine after the expiry date (EXP) stated on the container. Shelf life after opening- The prepared infusion solution of MabThera is physically and chemically stable for 24 hours at 2–8°C and for 12 hours at 15–25°C. From a microbiological point of view, the ready-to-use preparation should be used immediately after dilution. If this is not possible, post-preparation storage times and conditions prior to use are the responsibility of the user and should normally not be longer than 24 hours at 2–8°C unless dilution has taken place in controlled and validated aseptic conditions. Special precautions for storage-Store vials in a refrigerator (at 2–8°C). Keep the container in the outer carton in order to protect the contents from light. Keep medicines out of the reach of children." under this section.	15-Jan-21	Roche
8	Plavix	Clopidogrel	Special warnings and precautions for use	Addition of texts under Cytochrome P450 2C19 (CYP2C19) to include "Use of medicinal products that induce the activity of CYP2C19 would be expected to result in increased drug levels of the active metabolite of clopidogrel and might potentiate the bleeding risk. As a precaution concomitant use of strong CYP2C19 inducers should be discouraged (see section 4.5).	11-Jan-21	Sanofi
			Interaction with other medicinal products and other forms of interaction	Addition of texts under other concomittant therapy to include "Inducers of CYP2C19: Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that induce the activity of this enzyme would be expected to result in increased drug levels of the active metabolite of clopidogrel. Rifampicin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged (see section 4.4). Inhibitors of CYP2C19		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
9	Sayana Press	Medroxyprogesterone acetate	Special warnings and precautions for use	Reposition of texts to read "If any of the conditions/risk factors mentioned is present, the benefits of SAYANA PRESS use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether SAYANA PRESS use should be discontinued".	22-Jan-21	Pfizer
			Pharmacological properties	Revision of figures in table 2, 3 and 4		
10	Tecentriq	Atezolizumab	Qualitative and quantitative composition	Revision of text to read "After dilution (see section 6.6), the final concentration of the diluted solution should be between 3.2 and 16.8 mg/mL" under this section.	15-Jan-21	Roche
			Posology and method of administration	Revision of text to read "The safety and efficacy of Tecentriq in children and adolescents aged below 18 years have not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made" under Paediatric Population.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Tecentriq	Atezolizumab	Special warnings and precautions for use	Revision of text to read "Cases of pneumonitis, including fatal cases, have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis and causes other than immune-related pneumonitis should be ruled out" under Immune related Pneumonitis. Deletion of text "Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in metastatic non squamous non-small cell lung cancer. Physicians should carefully consider the combined risks of the four-drug regimen of atezolizumab, bevacizumab, paclitaxel and carboplatin before initiating treatment (see section 4.8)" under Disease Specific Precautions Revison of text to read "Neutropenia and peripheral neuropathies occurring during treatment with atezolizumab and nab-paclitaxel may be reversible with interruptions of nab-paclitaxel. Physicians should consult the nab-paclitaxel summary of product characteristics (SmPC) for specific precautions and contraindications of this medicine." under the sub- heading Use of atezolizumab in combination with nab-paclitaxel in metastatic triple negative breast cancer. Deletion of text "Patients with NSCLC that had clear tumour infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging, were excluded from the pivotal clinical study IMpower150 after several cases of fatal pulmonary haemorrhage were observed, which is a known risk factor of treatment with bevacizumab. In the absence of data, atezolizumab should be used with caution in these populations after careful evaluation of the balance of benefits and risks for the patient" under Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin. Deletion of text "In study IMpower150, there are no data on the efficacy of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in EGFR+ patients who have progressed previously on erlotinib+bevacizumab. " under the sub-heading Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in EGFR+ patients with NSCLC who have progressed on erlotinib+bevacizumab.	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Tecentriq	Atezolizumab	Undesirable effects	Revision of text to read "The safety of atezolizumab as monotherapy is based on pooled data in 3,568 patients across multiple tumour types. The most common adverse reactions (> 10%) were fatigue (34.5%), decreased appetite (24.0%), nausea (22.4%), pyrexia (20.1%), diarrhoea (19.9%), cough (19.8%), rash (19.8%), dyspnoea (19.0%), musculoskeletal pain (14.7%), back pain (14.4%), vomiting (14.1%), pruritus (14.0%) asthenia (13.9%), arthralgia (13.6%), urinary tract infection 13.1%) and headache (10.9%). The safety of atezolizumab given in combination with other medicinal products, has been evaluated in 3,878 patients across multiple tumour types. The most common adverse reactions (≥ 20%) were anaemia (40.3%), neutropenia (39.4%), nausea (37.3%), fatigue (34.4%), alopecia (29.6%), thrombocytopenia (28.9%), diarrhoea (28.1%), rash (27.7%), constipation (27.2%), peripheral neuropathy (25.7%), and decreased appetite (25.5%)" under Summary of the Safety Profile. Deletion of "blood alkaline phosphatase increased, blood creatine increasded" with frequency common under the System Organ Class Infections and Infestations under the heading Summary of adverse reactions occurring in patients treated with atezolizumab, Addition of "hyperthyroidism" with frequency common under the System Organ Class Endocrine Disorders under the heading Summary of adverse reactions occurring in patients treated with atezolizumab. Addition of "headache" with frequency very common under the System Organ Class Nervous System Disorders under the heading Summary of adverse reactions occurring in patients treated with atezolizumab, Addition of "uveitis" with frequency rare under the System Organ Class Eye Disorders under the heading Summary of adverse reactions occurring in patients treated with atezolizumab, Addition of "hypertension" with frequency very common under the System Organ Class Vascular Disorders under the heading Summary of adverse reactions occurring in patients treated with atezolizumab, Addition of "dry skin" with frequency common under the System Organ Class Skin and Subcutaneous Tissue Disorders under the heading Summary of adverse reactions occurring in patients treated with atezolizumab. Addition of "psoriasis" with frequency uncommon under the System Organ Class Skin and Subcutaneous Tissue Disorders under the heading Summary of adverse reactions occurring in patients treated wiith atezolizumab,	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Tecentriq	Atezolizumab	Undesirable effects	Addition of "blood creatinine increased" with frequency common under the System Organ Class Renal and Urinary Disorders under the heading Summary of adverse reactions occurring in patients treated wiith atezolizumab, Addition of blood alkaline phospahtase increased with frequncy common under the System Organ Class Investigations under the heading Summary of adverse reactions occurring in patients treated wiith atezolizumab, Addition of adverse reactions to legend in table 2 under the heading Summary of adverse reactions occurring in patients treated with atezolizumab. b- paracancerous pneumonia, pleural infection i- silent thyroiditis, thyroiditis chronic u- diarrhea haemorrhagic ac- urine abnormality ai- Includes reports of hypertension, blood pressure increased, hypertensive crisis, blood pressure systolic increased, diastolic hypertension, blood pressure inadequately controlled, retinopathy hypertensive Revision of text to read "Pneumonitis occurred in 2.8% (99/3,568) of patients who received atezolizumab monotherapy. Of the 99 patients, one experienced a fatal event. The median time to onset was 4.0 months (range 3 days to 24.8 months). The median duration was 1.6 months (range 0 day to 21.7+ months; + denotes a censored value). Pneumonitis led to discontinuation of atezolizumab in 15 (0.4%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.5% (53/3,568) of patients receiving atezolizumab monotherapy" under Immune-related Pneumonitis. Revision of text to read "Hepatitis occurred in 1.8% (66/3,568) of patients who received atezolizumab monotherapy. Of the 66 patients, two experienced a fatal event. The median time to onset was 1.5 months (range 6 days to 18.8 months). The median duration was 2.1 months (range 0 day to 22.0+ months; + denotes a censored value). Hepatitis led to discontinuation of atezolizumab in 9 (0.3%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.5% (19/3,568) of patients receiving atezolizumab monotherapy" under Immune-related hepatitis.	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Tecentriq	Atezolizumab	Undesirable effects	Revision of text to read 'Colitis occurred in 1.2% (43/3,568) of patients who received atezolizumab monotherapy. The median time to onset was 5.0 months (range 15 days to 17.2 months). The median duration was 1.2 months (range 3 days to 17.8+ months; + denotes a censored value). Colitis led to discontinuation of atezolizumab in 15 (0.4%) patients. Colitis requiring the use of corticosteroids occurred in 0.5% (19/3,568) of patients receiving atezolizumab monotherapy" under Immune-related colitis. Thyroid disorders- Revision of text to read"Hypothyroidism occurred in 6.0% (214/3,568) of patients who received atezolizumab monotherapy. The median time to onset was 4.4 months (range: 0 day to 31.3 months). Hyperthyroidism occurred in 1.3% (47/3,568) of patients who received atezolizumab monotherapy. The median time to onset was 2.1 months (range 21 days to 15.7 months)" under Immune-related endocrinopathies. Revision of text to read "Adrenal insufficiency occurred in 0.4% (13/3,568) of patients who received atezolizumab monotherapy. The median time to onset was 5.7 months (range: 3 days to 19 months). The median duration was 16.8 months (range: 0 day to 20.9+ months; + denotes a censored value). Adrenal insufficiency led to discontinuation of atezolizumab in 1 (<0.1%) patient. Adrenal insufficiency requiring the use of corticosteroids occurred in 0.3% (10/3,568) of patients receiving atezolizumab monotherapy" under Adrenal Insufficiency.	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Tecentriq	Atezolizumab	Undesirable effects	Revision of text to read 'Hypophysitis occurred in < 0.1% (3/3,568) of patients who received atezolizumab monotherapy. The median time to onset 5.3 months (range: 24 days to 13.7 months). Two (<0.1%) patients required the use of corticosteroids and treatment with atezolizumab was discontinued in 1 (<0.1%) patient. Hypophysitis occurred in 0.4% (2/473) of patients who received atezolizumab in combination with nab-paclitaxel and carboplatin. The median time to onset was 5.2 months (range: 5.1 to 5.3 months). Both patients required the use of corticosteroids" under Hypophysitis. Revision of text to read "Diabetes mellitus occurred in 0.3% (11/3,568) of patients who received atezolizumab monotherapy. The median time to onset was 4.2 months (range 3 days to 9.9 months). Diabetes mellitus requiring the use of corticosteroids occurred in < 0.1% (2/3,568) of patients receiving atezolizumab monotherapy. Diabetes mellitus led to the discontinuation of atezolizumab in < 0.1% (3/3,568) patients" under Diabetes mellitus. Revision of text to read "Meningoencephalitis occurred in 0.4% (14/3,568) of patients who received atezolizumab monotherapy. The median time to onset was 15 days (range: 0 day to 12.5 months). The median duration was 21 days (range 6 days to 14.5+ months; + denotes a censored value). Meningoencephalitis requiring the use of corticosteroids occurred in 0.2% (6/3,568) of patients receiving atezolizumab and four patients discontinued atezolizumab" under Immune-related meningoencephalitis .	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Tecentriq	Atezolizumab	Undesirable effects	Revision of text to read "Guillain-Barré syndrome and demyelinating polyneuropathy occurred in 0.1% (5/3,568) of patients who received atezolizumab monotherapy. The median time to onset was 7 months (range: 18 days to 8.1 months). The median duration was 8.0 months (range 18 days to 8.3+ months; + denotes a censored value). Guillain-Barré syndrome led to discontinuation of atezolizumab in 1 patient (< 0.1%). Guillain-Barré syndrome requiring the use of corticosteroids occurred in < 0.1% (2/3,568) of patients receiving atezolizumab monotherapy" under Immune-related neuropathies. Revision of text to read "Myasthenia gravis occurred in < 0.1% (1/3,568) of patients who received atezolizumab monotherapy. The time to onset was 1.2 months" under Myasthenic Syndrome. Revision of text to read "Pancreatitis, including amylase increased and lipase increased, occurred in 0.8% (27/3,568) of patients who received atezolizumab monotherapy. The median time to onset was 4.3 months (range: 0 days to 16.9 months). The median duration was 27 days (range 3 days to 22.4+ months; + denotes a censored value). Pancreatitis led to the discontinuation of atezolizumab in 3 (< 0.1%) patients. Pancreatitis requiring the use of corticosteroids occurred in 0.1% (4/3,568) of patients receiving atezolizumab monotherapy" under Immune-related Pancreatitis. Revision of text to read "Nephritis occurred in 0.2% (8/3,568) of patients who received atezolizumab. The median time to onset was 6.0 months (range: 2.0 to 17.5 months). Nephritis led to discontinuation of atezolizumab in 4/3,568 (0.1%) patients. Two (<0.1%) patients required corticosteroids" under Immune-related Nephritis.	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Tecentriq	Atezolizumab	Undesirable effects	Revision of text to read "Myositis occurred in 0.4% (15/3,568) of patients who received atezolizumab monotherapy. The median time to onset was 2.9 months (range: 0.4 to 11.0 months). The median duration was 3.8 months (range 3 days to 22.6+ months; + denotes a censored value). Myositis led to discontinuation of atezolizumab in 1 (<0.1%) patient. Seven (0.2%) patients required the use of corticosteroids" under Immune-related Myositis. Deletion of text" In the first-line NSCLC study (IMpower150), an overall higher frequency of adverse events was observed in the four-drug regimen of atezolizumab, bevacizumab, paclitaxel, and carboplatin compared to atezolizumab, paclitaxel and carboplatin, including Grade 3 and 4 events (63.6% compared to 57.5%), Grade 5 events (6.1% compared to 2.5%), adverse events of special interest to atezolizumab (52.4% compared to 48.0%), as well as adverse events leading to withdrawal of any study treatment (33.8% compared to 13.3%). Nausea, diarrhoea, stomatitis, fatigue, pyrexia, mucosal inflammation, decreased appetite, weight decreased, hypertension and proteinuria were reported higher (≥5% difference) in patients receiving atezolizumab in combination with bevacizumab, paclitaxel and carboplatin. Other clinically significant adverse events which were observed more frequently in the atezolizumab, bevacizumab, paclitaxel, and carboplatin arm were epistaxis, haemoptysis, cerebrovascular accident, including fatal events." under the sub-heading Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin . Revision of text to read "Across multiple phase III studies, 13.1% to 36.4% of patients developed treatment-emergent anti-drug antibodies (ADAs). Across pooled datasets for patients treated with atezolizumab monotherapy (N=2705) and with combination therapies (N=1811), the following rates of adverse events (AEs) have been observed for the ADA-positive population compared to the ADA-negative population, respectively: Grade 3-4 AEs 49.1% vs. 44.3%, Serious Adverse Events (SAEs) 42.4% vs. 37.6%, AEs leading to treatment withdrawal 6.1% vs 6.7% (for monotherapy); Grade 3-4 AEs 65.3% vs. 63.6%, SAEs 42.1% vs. 36.6%, AEs leading to treatment withdrawal 24.3% vs 19.5% (for combination therapy). However, available data do not allow firm conclusions to be drawn on possible patterns of adverse drug reactions" under Immunogenecity.	15-Jan-21	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Tecentriq	Atezolizumab	Undesirable effects	Addition of text "The safety of atezolizumab in children and adolescents has not been established. No new safety signals were observed in a clinical study with 69 paediatric patients (<18 years) and the safety profile was comparable to adults" under Paediatric Population. Revision of text to read "No overall differences in safety were observed between patients ≥ 65 years of age and younger patients receiving atezolizumab monotherapy" under Elderly Patients	15-Jan-21	Roche
			Pharmacological Properties	Addition of text "An exploratory updated survival analysis was performed with a median duration of survival follow up of 34 months in the ITT population. The median OS was 8.6 months (95% CI: 7.8, 9.6) in the atezolizumab arm and 8.0 months (95% CI: 7.2, 8.6) in the chemotherapy arm with a hazard ratio of 0.82 (95% CI: 0.71, 0.94). Consistent with the trend observed at primary analysis for 12-month OS rates, numerically higher 24-month and 30-month OS rates were observed for patients in the atezolizumab arm compared with the chemotherapy arm in the ITT population. The percentage of patients alive at 24 months (KM estimate) was 12.7% in the chemotherapy arm and 22.5% in the atezolizumab arm; and at 30 months (KM Addition of text: estimate) was 9.8% in the chemotherapy arm and 18.1% in the atezolizumab arm" under the sub-heading Urothelial carcinoma. Revision of text to read "An early phase, multi-centre open-label study was conducted in paediatric (<18, n=69) and young adult patients (18-30 years, n=18) with relapsed or progressive solid tumours as well as with Hodgkin's and non-Hodgkin's lymphoma, to evaluate the safety and pharmacokinetics of atezolizumab. Patients were treated with 15 mg/kg atezolizumab IV every 3 weeks (see section 5.2)" under the sub-heading Paediatric Population		
			Pharmacokinetic properties	Revision of text to read "The pharmacokinetic results from one early-phase, multi-centre open-label study that was conducted in paediatric (<18 years, n=69) and young adult patients (18-30 years, n=18), show that the clearance and volume of distribution of atezolizumab were comparable between paediatric patients receiving 15 mg/kg and young adult patients receiving 1,200 mg of atezolizumab every 3 weeks when normalized by body weight, with exposure trending lower in paediatric patients as body weight decreased. These differences were not associated with a decrease in atezolizumab concentrations below the therapeutic target exposure. Data for children <2 years is limited thus no definitive conclusions can be made" under Paediatric Population.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Tecentriq	Atezolizumab	Special precautions for disposal and other handling	Revision of text to read "For the recommended dose of 840 mg: fourteen mL of Tecentriq concentrate should be withdrawn from the vial and diluted into a polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), or polypropylene (PP) infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection. For the recommended dose of 1680 mg: twenty-eight mL of Tecentriq concentrate should be withdrawn from two vials of Tecentriq 840 mg and diluted into a polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), or polypropylene (PP) infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection. After dilution, the final concentration of the diluted solution should be between 3.2 and 16.8 mg/mL" under Instructions for Dilution.	15-Jan-21	Roche
11	Xolfovel	Levofloxacin	Special warnings and precautions for use	Addition of subheading to read "Risks of resistance" Addition of text under elderly patients to include "Levofloxacin treatment should be stopped immediately if a patient reports blood glucose disturbance and alternative nonfluoroquinolone antibacterial therapy should be considered" Revision of text under psychotic reactions to read "In the event that the patient develops these reactions, levofloxacin should be discontinued immediately at the first signs or symptoms of these reactions and the patient should be advised to contact their prescriber for advice. Alternative non-fluoroquinolone antibacterial therapy should be considered, and appropriate measures initiated.	22-Jan-21	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Xolfovel	Levofloxacin	Special warnings and precautions for use	Revision of text under Aortic aneurysm, dissection, and heart valve regurgitation/incompetence to read "Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.8). Therefore, fluoroquinolones should only be used after a careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection or heart valve disease, or in presence of other risk factors or conditions predisposing - for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behçet´s disease, hypertension, rheumatoid arthritis known atherosclerosis) or additionally - for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally - for heart valve regurgitation/incompetence (e.g. infective endocarditis)."	22-Jan-21	Sandoz
				Revision of text to read "The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids. In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department. Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities. under this section.		
			Undesirable effect	Revision of text under metabolism and nutrition disorders from "not known:hypogylcaemic coma" to "rare: hypoglycaemic coma"		
				Addition of text under psychiatric disorders to include "delirium"		
				Addition of text to include "Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4)." under this section.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
Safety Updates						
No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	Apidra	Insulin glulisine	need to know before you	Addition of text to include "Skin changes at the site of injection The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Apidra). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose." under subheading Warnings and precautions.	23-Mar-21	Sanofi-Aventis
			Possible side effects	Addition of text to include "Skin changes at the site of injection: if you inject insulin too often at the same place, the fatty tissue may either shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect up to 1 in 1,000 people). Lumps under the skin may also be caused by build-up of protein called amyloid (cutaneous amyloidosis; how often this may occur is not known). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes" under subheading Other side effects. Deletion of "Rare reported side effects (may affect up to 1 in 1,000 people) Skin changes at the injection site (lipodystrophy) If you inject you insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very. Changing the injection site with each injection may help to prevent such changes." under this section		
2	Daktarin oral gel	Miconazole	Before you use Daktarin oral gel	Revision of text to read "Daktarin oral gel contains 0.00785 g of alcohol (ethanol) in each 1 g which is equivalent to 0.00785 mg/mg (0.785 % w/w). The amount in 1 g is equivalent to less than 1 mL beer or 1 mL wine. The small amount of alcohol in this medicine will not have any noticeable effects. Daktarin oral gel contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'." under the subheading Important information about some of the ingredients of Daktarin oral gel.	15-Apr-21	Janssen

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Docetaxel	Docetaxel	What you need to know before you use docetaxel Sandoz	Addition of text to include "Tumor lysis syndrome may occur with use of docetaxel. The tumor cells release their contents into the bloodstream, either spontaneously or in response to treatment, leading high blood levels of uric acid, potassium, phosphates, and low calcium " under the sub-heading Warnings and precautions.	09-Oct-20	Sandoz
3	Docetaxel	Docetaxel	Possible side effects	Addition of side effects "• Tumor lysis syndrome • inflammation of muscles (myositis)" to text under the sub-heading Frequency unknown	09-Oct-20	Sandoz
4	Fluconazole	Fluconazole	What you need to know before you take Fluconazole Sandoz Capsule	Revision of text to read "Tolvaptan used to treat low levels of sodium in the blood. This results in a significantly increased risk of undesirable effects, especially diuresis, dehydration and acute renal failure" under Taking other medicines. Addition of text to read "Do not use Fluconazole Sandoz Capsule if you are pregnant, trying to get pregnant or are breast- feeding. Your doctor must weigh the mother's need for fluconazole and potential risk to the child from fluconazole or the underlying maternal condition" under Pregnancy and breast-feeding. Revision of text to read "Some thrush infections may be resistant to fluconazole. In such instances your doctor may prescribe an alternate antifungal" under Important information about some of the ingredients of Fluconazole Sandoz Capsule.	19-Mar-21	Sandoz
			Possible side effects	Revision of text to read "The following have been reported rarely by some patients, but it may not be due to this medicine: Skin disorders and unexpected bruising, drug reaction with eosinophilia and systemic symptoms (DRESS)" under this section.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Levetiracetam	Levetiracetam	What you need to know before you take Levetiracetam Sandoz	Addition of text to read "Talk to your doctor before taking Levetiracetam Sandoz: Levetiracetam may cause behavioral abnormalities including irritability and aggressiveness (psychotic symptoms). If any such behaviors are observed, please contact your doctor. Levetiracetam, as with other types of anti-epileptics, may rarely cause increase in seizure frequency or severity. This paradocixal effect, if it were to occur, usually happens in within the first month of starting the drug or increasing the dose and is reversible if the medication is stopped or dosage reduced. Rare cases of slowing down of the electrical activity of the heart has been in observed in some patients taking Levetiracetam and so is used with caution in patients with a history of abnormal heart electrical activity, patients using other drugs that may similarly cause the same symptoms, patients with relevant pre-existing cardiac disease or electrolyte imbalance" under sub-heading Warnings and precautions.	16-Apr-21	Sandoz
			How to take Levetiracetam Sandoz	Revision of text to read "Dose in infants (1 month to 23 months), children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg: Levetiracetam is not appropriate for initial treatment or dose adjustments in children and adolescents, for maintenance treatment of children and adolescents weighing less than 50 kg and also for patients unable to swallow tablets or for the administration of doses other than 750 mg or 1500 mg. Your doctor will prescribe the most appropriate pharmaceutical form of levetiracetam according to the age, weight and dose." under the sub-heading Add on therapy.		
			Possible side effects	Addition of side effects "encephalopathy, seizures aggravated and Electrocardiogram QT prolonged" under the sub-heading Rare.		
6	Levetiracetam	Levetiracetam	What you need to know before you take Levetiracetam Sandoz	Addition of text to read "Levetiracetam may cause behavioral abnormalities including irritability and aggressiveness (psychotic symptoms). If any such behaviors are observed, please contact your doctor." under the sub-heading Warnings and Precautions:Talk to your doctor before taking Levetiracetam Sandoz.	05-Feb-21	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Lipitor	Atorvastatin	Special warnings and precautions for use	Addition of text to read "There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins (see section 4.8. Undesirable effects). IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment, positive anti-HMG CoA reductase antibody and improvement with immunosuppressive agents." under sub-heading Skeletal muscle effects.	01-Apr-21	Pfizer
			Pharmaceutical particulars	Revision of texts to read "Blister packs containing 30 and 100 film-coated tablets. Not all strengths and/or pack sizes may be marketed." under sub-heading Nature and contents of container.		
8	Nasonex	Mometasone furoate	What you need to know before you use Nasonex	Revision of text to read "Benzalkonium chloride may cause irritation or swelling inside the nose, especially if used for a long time" under the sub-heading Nasonex contains benzalkonium chloride.	07-Apr-21	MSD
			Possible side effects	Revision of text to read "If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. " under the sub-heading Reporting side effects.		
			Contents of the pack and other information	Addition of text "This medicine contains 0.02mg of bezalkonium chloride per spray" under What Nasonex Contains.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
9	Piperacillin/ Tazobactam	Piperacillin/ tazobactam	What you need to know before you use Piperacillin Tazobactam Sandoz	Revision of text to read "Tell your doctor or other healthcare professional if you are taking, or have recently taken or might take any other medicines, including medicines obtained without a prescription. under the subheading other medicines and piperacillin tazobactam sandoz. Revision of text to read "Some medicines may interact with piperacillin and tazobactam. These include: medicines containing the other antibiotics tobramycin, gentamycin or vancomycin. There may be an increased risk of developing kidney problems with concomitant use of vancomycin and Piperacillin Tazobactam. Tell your doctor if you have kidney problems." under the subheading other medicines and piperacillin tazobactam sandoz. Revision of text 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 other healthcare professional for advice before receiving this medicine. Your doctor will decide if Piperacillin Tazobactam Sandoz is right for you. Piperacillin and tazobactam can pass to a baby in the womb or through breast milk. If you are breast-feeding, your doctor will decide if Piperacillin Tazobactam Sandoz is right for you." under the subheading pregnancy and breastfeeding Revision of texts to read "Piperacillin Tazobactam Sandoz 2 g / 0.25 g contains109 mg of sodium (main component of cooking/table salt) in each dosage unit. This is equivalent to 6% of the recommended maximum daily dietary intake of sodium for an adult. Piperacillin Tazobactam Sandoz 4 g / 0.5 g contains 217 mg of sodium (main component of cooking/table salt) in each dosage unit. This is equivalent to 11% of the recommended maximum daily dietary intake of sodium for an adult. This should be taken into consideration if you are on a controlled sodium diet." under this section.	19-Mar-21	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
9	Piperacillin/ tazobactam	Piperacillin/ tazobactam	Possible side effects	Revision of texts to read "serious skin rashes [Stevens-Johnson syndrome, dermatitis bullous (Not known), dermatitis exfoliative (Not known) toxic epidermal necrolysis (Rare)] appearing initially as reddish target-like spots or circular patches often with central blisters on the trunk. Additional signs include ulcers in the mouth, throat, nose, extremities, genitals and conjunctivitis (red and swollen eyes). The rash may progress to widespread blistering or peeling of the skin and potentially may be life threatening." under subheading The serious side effects (with frequency in brackets) of Piperacillin Tazobactam Sandoz are:. Deletion of texts that read "If any of the following side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or other healthcare professional." under subheading The serious side effects The serious side effects (with frequency in brackets) of Piperacillin Tazobactam Sandoz are:. Revision of texts to read " - decrease in platelets decrease of red blood cells or blood pigment / haemoglobin, abnormal lab test (positive direct Coombs), prolonged blood clotting time (activated partial thromboplastin time prolonged) - rash, itching" under the sub-heading common side effects (may affect up to 1 in 10 people). Revision of texts to read "- inflammation of the large intestine (colon) due to over growth of bacteria " under sub-heading Rare side effects. Deletion of "- detachment of the top layer of the skin all over the body (toxic epidermal necrolysis) " from text under the sub-heading Rare side effects.	19-Mar-21	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
9	Piperacillin/ tazobactam	Piperacillin/ tazobactam	Possible side effects	Revision of text to read "- severe decrease of red blood cells, white blood cells and platelets (pancytopenia), decrease in white blood cells (neutropenia), decrease of red blood cells due to premature breakdown or degradation, bleeding time prolonged, increase of platelets, increase of a specific type of white blood cells (eosinophilia) - allergic reaction and severe allergic reaction - jaundice, inflammation of the liver, increase in blood liver enzyme - poor kidney functions and other kidney problems - severe skin reactions and disorders of the membrane lining body cavities (mucous membrane) characterized by redness, blistering, skin peeling - a form of lung disease where eosinophils (a form of white blood cell) appear in the lung in increased numbers. Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients." under the sub-heading Not known side effects. Revision of texts to read "You can also report side effects directly via: drug.safetyssa.novartis.com." under the subheading Reporting of side effects.	19-Mar-21	Sandoz
10	Pregabalin	Pregabalin	What you need to know before you take Pregabalin Sandoz	Addition of texts to include "Severe respiratory depression may occur. Patients with compromised respiratory, neurological, or renal impairment and the elderly might be more at risk" under the subheadingWarnings and precautions. Addition of text to include "Caution is advised when prescribing pregabalin concomitantly with Opiods even at low doses of pregabalin" under subheading Other medicines and Pregabalin Sandoz	14-Dec-20	Sandoz
			Possible side effects	Addition of text to include "Not known (cannot be estimated from the available data): • Difficulty breathing (Respiratory depression)" under this section		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Vancomycin	Vancomycin	What Vancomycin Sandoz® is and what it is used for	Revision of text to read " Vancomycin is an antibiotic that belongs to a group of antibiotics called “glycopeptides”. Vancomycin works by eliminating certain bacteria that cause infections. Vancomycin is used in all age groups by infusion for the treatment of the following serious infections: • Infections of the skin and tissues below the skin. • Infections of bone and joints. • An infection of the lungs called "pneumonia” • Infection of the inside lining of the heart (endocarditis) and to prevent endocarditis in patients at risk when undergoing major surgical procedures • Infection in central nervous system. • Infection in the blood linked to the infections listed above Vancomycin can be used in adults and children from birth onwards. It can also be given to you before some surgical procedures to prevent infections. Your medicine is in the form of a powder for solution. Before use, it will be dissolved and diluted with an intravenous fluid that will be given to you slowly by a drip into your vein by a doctor or nurse." under this section.	02-Mar-21	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Vancomycin	Vancomycin	What you need to know before you take Vancomycin Sandoz®	Addition of text "If you have disorders or infections of the eye as this may lead to further complications and permanent loss of vision" under Do not take Vancomycin Sandoz. Revision of text to read "Talk to your doctor or hospital pharmacist or nurse during treatment with Vancomycin if: -You are receiving vancomycin for a long time (you may need to have your blood, hepatic and kidneys tested during treatment). -You develop any skin reaction during the treatment. -You develop severe or prolonged diarrhoea during or after using vancomycin, consult your doctor immediately. This may be a sign of bowel inflammation (pseudomembranous colitis) which can occur following treatment with antibiotics. It is advised that vancomycin levels in the blood should be monitored during treatment. Stop treatment with Vancomycin immediately and talk to your doctor if: - You develop any skin reaction during the treatment" under the sub-heading Warnings and precautions. Revision of text to read "The following can react with vancomycin if you take them at the same time, such as medicines for the treatment of: Infections caused by Bacteria-? infections caused by bacteria (streptomycin, neomycin, gentamicin, kanamycin, amikacin, bacitracin, tobramycin, polimyxin B, piperacillin/tazobactam, colistin)"under Other medicines and Vancomycin Sandoz.	02-Mar-21	Sandoz
			How you are given Vancomycin Sandoz	Revision of text to read " Children aged from one month to less than 12 years of age: The dosage will be calculated according to your body weight. The usual infusion dose is 10 to 15 mg for each kg of body weight. It is usually given every 6 hours. Kidney damage has been reported in children usually when vancomycin is used in association with other nephrotoxic agents." under the sub heading Use in Children.		
			Possible Side Effects	Addition of adverse effects "Blisters, rash and inflammation of the lining of the mouth, itching, itching rash; hives"under Common Side Effects.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Vancomycin	Vancomycin	Contents of the pack and other information	Revision of text to read " The active substance is vancomycin hydrochloride. Each vial Vancomycin Sandoz® contains 500 mg vancomycin (hydrochloride) equivalent to 500,000 IU. Each vial Vancomycin Sandoz® contains 1000 mg vancomycin (hydrochloride) equivalent to 1,000,000 IU. There are no other ingredients."under the heading What Vancomycin Sandoz® contains.	02-Mar-21	Sandoz
12	Velcade	Bortezomib	Possible side effects	Addition of texts to read "Serious nerve inflammation, which may cause paralysis and difficulty breathing (Guillain-Barré syndrome)" under the sub-heading Rare side effects.	15-Apr-21	Janssen
13	Vinorelbine	Vinorelbine	Possible side effects	Revision of text to read" Not known (frequency cannot be estimated from the available data):Symptoms of an allergic or anaphylactic reaction with sudden signs such as rash, itching or hives on the skin, difficulties in swallowing, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing, extreme tiredness (you may feel you are going to faint), low levels of white cells in the blood (leukopenia), headache and dizziness. Heart failure, abdominal pain"under the sub-heading Serious side effects – if any of the following side effects happen, please tell your doctor immediately.	18-Feb-21	Sandoz