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	Actemra	Tocilizumab	Dosage	Revision of text under subtitle Intravenous(IV) formulation to read "The i.v. formulation of Actemra is not intended for subcutaneous administration".	17/05/2022	Roche
			Special dosage instructions	Revision of text under subtitle Patients with renal impairment to read"No dose adjustment is required in patients with mild or moderate renal impairment. Actemra has not been studied in patients with severe renal impairment."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	Actemra	Tocilizumab	Warnings and precautions	Revision of text under subtitle Infections to read "Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab. Actemra should not be administered to patients with active infection. Patients with recurrent infections or with underlying diseases predisposing to infection (e.g. diverticulitis, diabetes and interstitial lung disease) should be treated with caution. Increased vigilance for timely detection of serious infection is recommended for patients treated with immunosuppressants such as Actemra for moderate to severe RA, PJIApJIA, sJIA or SJIAGCA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants. When investigating a patient for suspected infection, it is important to bear in mindmin d the impact of IL -6 inhibition on C -reactive protein (CRP) and neutrophils. Inhibition of IL -6 may weaken the response to infection as manifested by the CRP concentration and neutrophil count. Patients (including younger children who may be less able to communicate their symptoms) and parents/guardians of minors should be instructed to contact a healthcare professional immediately when any symptoms suggesting infection appear, in order to ensure rapid evaluation and appropriate treatment."	17/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	Actemra	Tocilizumab	Warnings and precautions	Revision of text under subtitle Hepatoxicity to read"An increase in transaminases may occur during Actemra therapy, in particular during coadministration with MTX. For this reason, caution is essential when administering Actemra to patients with active hepatic disease or hepatic impairment. A mild to moderate, transient and sometimes recurrent increase was observed in transaminases (ALT or AST) during Actemra therapy (see "Undesirable effects). "). An increased frequency of these elevated values was observed when using medicinal products known to be hepatotoxic (e.g. methotrexate [(MTX]) in combination with tocilizumab. Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, has been observed with Actemra (see "Undesirable effects)."). Serious hepatic injury occurred from 2 weeks to more than 5 years after initiation of Actemra. Cases of liver failure requiring liver transplantation have been reported. For dose modification recommendations, including Actemra withdrawal, for patients with elevated transaminase levels, see "Dosage/Administration".	17/05/2022	Roche
			Pregnancy and Lactation	Revision of text under subtitle Pregnancy to read"Insufficient data are available to support use of Actemra in pregnant women. A study in monkeys produced no evidence of teratogenic potential, but showed a greater number of spontaneous abortions/embryofetal deaths at high dose. The potential risk to humans is unknown. Actemra must not be administered during pregnancy unless the prescribing physician considers its use clearly necessary.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	Actemra	Tocilizumab	Undesirable effects	Revision of text to read" The safety profile in this section comes from 4510 patients treated with tocilizumab in clinical trials; the majority of these patients were participating in RA studies (n=4009),while the remaining data come from pJIA (n=240), sJIA (n=112) and GCA (n=149) studies. The safety profile of tocilizumab across these indications remains similar and undifferentiated. The adverse drug reactions (ADRs) are listed by MedDRA system organ class and according to their clinical importance to the patient. The respective frequency category for each undesirable effect is based on the following convention: 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), not known (frequency cannot be determined from post- marketing experience)." Revision of text under subtitle Skin and subcutaneous tissue disorders to read " Common: cellulitis, rash, pruritus, urticaria. Rare: Stevens-Johnson syndrome (SJS) (identified in post-marketing use). Renal and urinary disorders Uncommon: nephrolithiasis."	17/05/2022	Roche
			Immunogenicity	Revision of text to read "In the three studies in pJIA patients, a total of six patients (0.5% [1/188] in the i.v. study WA19977 and 9.6% [5/52] in the s.c. studies WA28117 and WA29231) developed positive neutralising anti-tocilizumab antibodies; none of these patients experienced a serious or clinically significant hypersensitivity reaction. Three of these six patients subsequently withdrew from the study. No correlation was observed between antibody development and clinical response or adverse events."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	Actemra	Tocilizumab	Description of selected adverse drug reactions from clinical studies	Revision of text under subtitle Polyarticular juvenile idiopathic arthritis to read" The safety profile of tocilizumab was studied in 240 paediatric patients with pJIA. In study WA19977,188 patients (2 to 17 years of age) were treated with i.v. tocilizumab, and in study WA28117, 52 patients (1 to 17 years of age) were treated with s.c. tocilizumab. Total exposure in the population of all pJIA patients exposed to tocilizumab was 184.4 patient-years. for i.v. tocilizumab and 50.4 patient-years for s.c. tocilizumab. In general, the safety profile observed in patients with pJIA was consistent with the known safety profile of tocilizumab with the exception of injection site reactions (see Table 1), although quantitatively more cases of neutropenia and neutralising antibodies were observed with subcutaneous Actemra administration (see also further below). A higher frequency of injection site reactions was observed in pJIA patients following s.c. tocilizumab injections than in adult RA patients (see “Undesirable effects). "	17/05/2022	Roche
			Systemic juvenile idiopathic arthritis	Revision of text to read "The safety profile of tocilizumab in sJIA was studied in 163 paediatric patients . In study WA18221 (12 - week study with long-term follow-up), 112 patients (2 to 17 years old) were treated with i.v. tocilizumab, and in study WA28118 (52-week study), 51 patients (1 to 17 years old) were treated with s.c. tocilizumab. During the phase I study (NP25737), no new or unexpected adverse reactions were observed in eleven paediatric sJIA patients under 2 years old. However, the incidence of serious hypersensitivity 3/11 (27%), including anaphylaxis, in these patients was higher than in sJIA patients aged 2 years and above.In general, the adverse drug reactions in patients with sJIA were similar to those observed in patients with RA (see “Undesirable effects” above).		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Avastin	Bevacizumab (manufactured by recombinant DNA technology using CHO [Chinese hamster ovary]	Infusion reaction	Revision of text under the subtitle Infusion reaction to read"In sJIA patients, infusion-related reactions are defined as all events occurring during an infusion of i.v. tocilizumab. or in the 24 hours thereafter. In the 12-week controlled study (WA18221), such events occurred in four percent (4.0%) of patients in the tocilizumab group during the infusion, with one event (angioedema) considered serious and life- threatening, resulting in discontinuation of the study treatment in that patient. An event occurred within 24 hours of infusion in 16% of patients in the group treated with i.v. tocilizumab and in 5.4% of patients in the placebo group. Events in the tocilizumab group, included rash, urticaria, diarrhoea, epigastric discomfort, arthralgia and headache. One of these events (urticaria) was classified as serious. Clinically significant hypersensitivity reactions associated with i.v. tocilizumab and requiring treatment withdrawal were reported in 1 of 112 patients (less than 1%) treated with i.v. tocilizumab in the controlled and open-label phases of the clinical trial."	18/05/2022	Roche
			Warnings and precautions	Revision of text under the subtitle Gastrointestinal perforation and fistula to read "Patients may be at increased risk of developing gastrointestinal perforation and gall bladder perforation if treated with Avastin (seeUndesirable effects). Avastin must be permanently discontinued in patients developing gastrointestinal perforation. Patients with persistent, recurrent, or metastatic cervical cancer treated with Avastin may be at increased risk of developing fistulae between the vagina and gastrointestinal tract (gastrointestinal- vaginal fistulae; see Undesirable effects)".		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Avastin	Bevacizumab (manufactured by recombinant DNA technology using CHO [Chinese hamster ovary]	Warnings and precautions	Revision of subtitle to read" Non-gastrointestinal fistulae" Revision of text under the subtitle Hypertensive encephalopathy to read"Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal. The symptoms of hypertensive encephalopathy include headache, decreased attention, confusion or stupor, with or without convulsions (see“Undesirable effects and Hypertension)." Revision of text under the subtitle Congestive health failure to read"Events consistent with congestive heart failure (CHF) were reported in clinical trials. Symptoms ranged from an asymptomatic decrease in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring treatment or hospitalisation. Most of the patients with CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or had other risk factors for CHF, such as pre- existing coronary heart disease or concomitant cardiotoxic therapy (see “Undesirable effects”). Caution is advised when treating patients with clinically relevant cardiovascular disease or pre-existing CHF with Avastin."	18/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Avastin	Bevacizumab (manufactured by recombinant DNA technology using CHO [Chinese hamster ovary]	Warnings and precautions	Revision of text under the subtitle Hypersensitivity reactions/infusion reactions to read"Hypersensitivity reactions/infusion reactions occurred frequently (in up to 5% of patients treated with bevacizumab) in some clinical trials. Infusion reactions reported in clinical trials and postmarketing experience included hypertension, hypertensive crises associated with neurological signs and symptoms, wheezing, oxygen desaturation, NCI-CTC Grade 3 hypersensitivity, chest pain, headaches, flu symptoms and diaphoresis. Symptoms can occur during or immediately after the infusion, or up to 2 days later. It is recommended that patients be closely monitored during and after Avastin administration. Avastin infusion should be discontinued and appropriate drug therapy administered if serious infusion reactions/hypersensitivity reactions occur. No data are available on the use of premedication. There are likewise no data regarding the most appropriate method for identifying patients who may safely be re-treated with Avastin after a serious infusion reaction."	18/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Avastin	Bevacizumab (manufactured by recombinant DNA technology using CHO [Chinese hamster ovary]	Warnings and precautions	Revision of text under subtitle Immunogenicity to read"Patients from two phase III studies on the adjuvant treatment of colon cancer were screened by immunoassay for anti-Avastin antibodies. Of the 2233 patients , 14 were found to be positive (0.6%), three of whom showed neutralising antibodies. The clinical significance of ansuch immune reaction to Avastin is unknown. However, none of theno adverse eventsevent in patientsany patient developing anti-Avastin antibodies showed any relationship towith a type I hypersensitivity reaction or to a type III immune complex-mediated reaction. Immunogenicity data are highly dependent on the sensitivity and specificity of the assay employed and may be influenced by several factors, including sample handling, timing of sample collection, drug interactions, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of anti-Avastin antibodies in different indications or with the incidence of antibodies to other therapeutic proteins may be misleading." Revision of text under subtitle Eye disorders to read "Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of Avastin. These included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, intraocular haemorrhage such as haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness."	18/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Avastin	Bevacizumab (manufactured by recombinant DNA technology using CHO [Chinese hamster ovary]	Undesirable effects	Revision of text under the subtitle Haemorrhage to read "In clinical trials across all indications, the overall incidence of NCI-CTC Grade 3–-5 bleeding events ranged from 0.4% to 6.9% in Avastin -treated patients, compared with 0% to 4.5% of patients in the chemotherapy control group. Tumour-associated haemorrhage (see below) and mild mucocutaneous bleeding (e.g. epistaxis) accounted for the majority of bleeding events observed." Revision of text under subtitle Gastrointestinal disorders "Common" to read "intestinal perforation, ileus, intestinal obstruction, rectovaginal (fistulae (occurring most commonly in the enterovaginal fistula category), gastrointestinal disorder, stomatitis, proctalgia" Revision of text under subtitle Non-gastrointestinal fistulafistulae (see “Warnings and precautions") to read"Avastin has been associated with serious cases of fistula, including events resulting in death. In a trial in patients with persistent, recurrent, or metastatic cervical cancer (GOG-0240), 1.8% of Avastin -treated patients and 1.4% of control patients developed vaginal, vesical, or genital fistulae unconnected to the gastrointestinal tract. Uncommon (≥0.1% to <1%) reports of other types of fistula (e.g. tracheo-oesophageal, bronchopleural, urogenital and biliary fistula) were observed across various indications. Events were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of Avastin, with most cases occurring within the first 6 months of therapy	18/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Benylin Dry Cough	Dextromethorphan hydrobromide	Posology and method of administration	Revision of text to read " Do not exceed the recommended dose. For oral use only. Shake the bottle before use. Adults: One medicine measure (5 mL) every four hours, or two medicine measures (10 mL) every six to eight hours. Children 5 to 12 years: Half to one medicine measure (2.5 mL – 5 mL) every six to eight hours. Children below 5 years of age: Not recommended (see section 4.3)."	25/05/2022	Johnson &Johnson
			Contraindications	Revision of text to read "Hypersensitivity to dextromethorphan or to any of the other ingredients in BENYLIN® DryCough (see section 6.1). Patients taking monoamine oxidase inhibitors (MAOIs), or for 2 weeks after stopping the MAOI medicine. There is risk of serotonin syndrome with the concomitant use of BENYLIN®Dry Cough and MAOIs and the concomitant use of these medicines may cause a rise in blood pressure and/or hypertensive crisis (see section 4.5). Patients with asthma and hepatic dysfunction. Children under 5 years of age."		
			Special warnings and precautions for use	Revision of text under subtitle Sodium benzoate to read "BENYLIN® Dry Cough contains sodium benzoate. An increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue)."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Benylin Dry Cough	Dextromethorphan hydrobromide	Special warnings and precautions for use	Revision of text to read " BENYLIN® Dry Cough should not be taken for a persistent respiratory condition, which occurs with smoking, bronchial asthma, emphysema, chronic bronchitis or where cough is by excessive secretions, except under the advice and supervision of a doctor. A persistent cough may be a sign of a serious condition. If cough persists for more than one week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a doctor. Persistent coughs should be investigated by a doctor for the possible underlying cause. Cases of dextromethorphan abuse and associated dependence have been reported. Caution with BENYLIN® Dry Cough is particularly recommended for adolescents and young adults, as well as in patients with a history of drug abuse or use of psychoactive substances. Dextromethorphan is metabolised by hepatic cytochrome P450 2D6. Poor metabolisers and patients with concomitant use of CYP2D6 inhibitors may experience exaggerated and/or prolonged effects of dextromethorphan.	25/05/2022	Johnson &Johnson
				Caution with BENYLIN® Dry Cough should therefore be exercised in patients who are slow metabolisers of CYP2D6 or use CYP2D6 inhibitors (see section 4.5). If a patient is a known slow metaboliser of CYP2D6, or is using any other medicines (such as serotonergic medicines, including selective serotonin re-uptake inhibitors (SSRIs), medicines which impair the metabolism of serotonin (including MAOIs - see section 4.3) or CYP2D6 inhibitors), a doctor or pharmacist should be consulted prior to taking BENYLIN® Dry Cough. Serotonergic effects, including the development of a potentially life-threatening serotonin syndrome, have been reported for dextromethorphan with concomitant administration of serotonergic medicine		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Benylin Dry Cough	Dextromethorphan hydrobromide	Interaction with other medicines and other forms of interaction	Revision of text under subtitle Monoamine oxidase inhibitors (MAOIs) to read"BENYLIN® Dry Cough should not be used concurrently in patients taking MAOIs, or within 14days of stopping treatment with MAOIs, as there is a risk of serotonin syndrome. Concurrent use with monoamine oxidase inhibitors may cause excitation, hypertension and hyperpyrexia." Revision of text under subtitle Central nervous system (CNS) depressants to read "Concomitant administration with central nervous system depressants may potentiate central nervous system depressant effects." Addition of text under title CYP450 interactions under subtitle CYP2D6 inhibitors to read"BENYLIN® Dry Cough is metabolised by CYP2D6 and has an extensive first-pass metabolism.Concomitant use of potent CYP2D6 enzyme inhibitors can increase the dextromethorphan concentrations in the body. This increases the risk of the patient for toxic effects of dextromethorphan (agitation, confusion, tremor, insomnia, diarrhoea and respiratory depression) and development of serotonin syndrome. Potent CYP2D6 enzyme inhibitors include fluoxetine, paroxetine, quinidine and terbinafine. In concomitant use with quinidine, plasma concentrations of dextromethorphan have increased up to 20-fold, which increases the CNS adverse effects of the medicine. Amiodarone, flecainide and propafenone, sertraline, bupropion, methadone, cinacalcet, haloperidol, perphenazine and thioridazine also have similar effects on the metabolism of dextromethorphan. If concomitant use of CYP2D6 inhibitors and BENYLIN® Dry Cough is necessary, the patient should be monitored and the BENYLIN® Dry Cough dose may need to be reduced."	25/05/2022	Johnson &Johnson

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Benylin Dry Cough	Dextromethorphan hydrobromide	Interaction with other medicines and other forms of interaction	Addition of text under subtitle Isavuconazole to read "Isavuconazole is a moderate inhibitor of CYP3A4 and a mild inducer of CYP2B6. When administered concomitantly with dextromethorphan, the area under the curve (AUC) and Cmax of dextromethorphan has been observed to increase by 18 % and 17 %, respectively. Addition of text under title Selective serotonin reuptake inhibitors (SSRIs) to read "Concomitant use of BENYLIN® Dry Cough with SSRI medicines may lead to serotonin syndrome"	25/05/2022	Johnson &Johnson
			Undesirable effects	Revision of text under subtitle Immune system disorders to read "Less frequent: angioedema" Revision of text under subtitle Psychiatric disorders to read "Less frequent: insomnia" Revision of text under subtitle Nervous system disorders to read "Less frequent: dizziness, psychomotor hyperactivity, somnolence" Revision of text under subtitle Gastrointestinal disorders to read "Less frequent: gastrointestinal disturbances, abdominal pain, diarrhoea,nausea, vomiting" Revision of text under subtitle Skin and subcutaneous tissue disorders to read "Less frequent: pruritus, rash, urticaria"		
			Reporting of suspected adverse reactions:	Addition of subtitle Reporting of suspected adverse reactions to read "Reporting suspected adverse reactions after authorisation of BENYLIN® Dry Cough is important. It allows continued monitoring of the benefit/risk balance of BENYLIN® Dry Cough. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8. For further information, please contact the Johnson & Johnson call centre on 0860 410032 (landline)"		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Benylin Dry Cough	Dextromethorphan hydrobromide	Overdose	Revision of text to read "Symptoms of overdose may include: excitation, agitation, confusional state, conversion disorder,mixed hallucinations, ataxia, clumsiness, coma, depressed levels of consciousness,dysarthria,dystonia, lethargy, nystagmus, seizure, serotonin syndrome, tremor, miosis, mydriasis,respiratory depression, urinary retention, tachycardia, ischaemic colitis, and hypertension. Bromide intoxication has been observed during concomitant use with bromide-containing over-thecounter medicines or with overdose of dextromethorphan hydrobromide."	25/05/2022	Johnson &Johnson
4	Benylin Paediatric syrup	Diphenhydramine hydrochloride 7mg	Contraindications	Revision of text to read "Known hypersensitivity to diphenhydramine hydrochloride or to any of the other ingredients in BENYLIN® PAEDIATRIC (see section 6.1). Diphenhydramine hydrochloride should not be used with monoamine oxidase inhibitors or within 14 days of stopping monoamine oxidase inhibitor treatment. Contraindicated during acute asthmatic attacks, and in patients with impaired hepatic or renal function. BENYLIN® PAEDIATRIC should not be used in children below 6 years of age."	26/05/2022	Johnson &Johnson
			Special warnings and precautions for use	Revision of text to read " BENYLIN® PAEDIATRIC may lead to drowsiness and impaired concentration which may be aggravated by the simultaneous intake of alcohol or other central nervous system depressant medicines. In infants and children, it may act as a cerebral stimulant. Symptoms of stimulation include insomnia, nervousness, tachycardia, tremors and convulsions. Large doses may precipitate fits in epileptics.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Benylin Paediatric syrup	Diphenhydramine hydrochloride 7mg	Special warnings and precautions for use	Deepening coma, extrapyramidal effects and photosensitization of the skin may occur. Elderly patients are more susceptible to the central nervous system depressant and hypotensive effects. Do not use with any other product containing diphenhydramine even ones used on skin. The positive results of skin tests may be suppressed. Diphenhydramine hydrochloride has anticholinergic properties and should be used with care in conditions such as a respiratory condition including emphysema (adult products), chronic bronchitis, or acute or chronic bronchial asthma, glaucoma, urinary retention and prostatic hypertrophy. Diphenhydramine hydrochloride should be used with caution in patients with liver impairment or cardiovascular disease. Patients should not use BENYLIN® PAEDIATRIC for persistent or chronic cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a physician. BENYLIN® PAEDIATRIC contains sugar: sucrose and glucose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take BENYLIN® PAEDIATRIC. BENYLIN® PAEDIATRIC contains sodium benzoate. An increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue)."	26/05/2022	Johnson &Johnson
			Fertility, pregnancy and lactation	Revision of text to read "Safety in pregnancy and lactation has not been established. Diphenhydramine crosses the placenta and is excreted into breast milk."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4.0	Benylin Paediatric syrup	Diphenhydramine hydrochloride 7mg	Effects on ability to drive and use machines	Revision of text to read" BENYLIN® PAEDIATRIC may cause drowsiness, dizziness or blurred vision. Patients should be warned not to drive a motor vehicle, operate dangerous machinery or climb dangerous heights as impaired decision making could lead to accidents."	26/05/2022	Johnson &Johnson
			Undesirable effects	Revision of text under subtitle Blood and the lymphatic system disorders to read "Less frequent: thrombocytopenia Frequency unknown: agranulocytosis, leucopenia and haemolytic anaemia" Revision of text under subtitle Immune system disorders to read" Frequency unknown: allergic reactions, anaphylaxis" Revision of text under subtitle Endocrine disorders to read"Less frequent: epigastric pain" Revision of text under subtitle Metabolism and nutrition disorders to read"Less frequent: anorexia, increased appetite" Revision of text under subtitle Psychiatric disorders to read "Less frequent: euphoria, confusional state, irritability, hallucination, nervousness" Revision of text under subtitle Nervous system disorders to read"Frequent: sedation Less frequent: headache, agitation, abnormal coordination, convulsion, dizziness,insomnia, paraesthesia, somnolence, tremor"		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Benylin Paediatric syrup	Diphenhydramine hydrochloride 7mg	Overdose	Revision of text under subtitle Diphenhydramine hydrochloride to read"Overdosage may be fatal especially in infants and children. In infants and children CNS stimulation predominates over CNS depression causing ataxia, excitement, tremors, psychoses, hallucinations and convulsions; hyperpyrexia may also occur. Deepening coma and cardiorespiratory collapse may follow. In adults: CNS depression with drowsiness, coma and convulsions, progressing to respiratory failure or possibly cardiovascular collapse. Treatment is symptomatic and supportive."	26/05/2022	Johnson &Johnson
5	Benylin Wet Cough Menthol syrup	Guaifenesin	Contraindications	Revision of text to read " •Hypersensitivity to guaifenesin or to any of the other ingredients in Benylin Wet Cough Menthol (see section 6.1). • Pregnancy and lactation (see section 4.6). "	27/05/2022	Johnson &Johnson
			Special warnings and precautions for use	Addition of text under subtitle Benylin Wet Cough Menthol contains sugar: sucrose and glucose to read "Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Benylin Wet Cough Menthol." Addition of text under subtitle Benylin Wet Cough Menthol contains sodium benzoate to read"An increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue)." Addition of text under subtitle Benylin Wet Cough Menthol contains sodium to read"Benylin Wet Cough Menthol contains 114 mg sodium per 10 mL, equivalent to 5,7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Benylin Wet Cough Menthol syrup	Guaifenesin	Fertility, pregnancy and lactation	Addition of text to read"Benylin Wet Cough Menthol should not be taken for persistent or chronic cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a physician. A persistent cough may be a sign of a serious condition. If cough persists for more than 7 days, tends to recur, or is accompanied by a fever, rash, or persistent headache, a doctor should be consulted."	27/05/2022	Johnson &Johnson
				Revision of text to read"Benylin Wet Cough Menthol should not be used during pregnancy and lactation (see section 4.3)"		
			Effects on ability to drive and use machines	Addition of subtitle to read "Effects on ability to drive and use machines" Addition of text to subtitle to read "Benylin Wet Cough Menthol can cause side effects, such as drowsiness and may affect the ability to drive and use machinery. Caution is advised before driving a vehicle or operating machinery until the effects of Benylin Wet Cough Menthol are known."		
			Undesirable effects	Revision of text to read "The safety of guaifenesin is based on available data from clinical trials and adverse drug reactions (ADRs) identified during post-marketing experience.The frequencies are provided according to the following convention: Very common ≥1/10, Common ≥1/100 and < 1/10, Uncommon ≥1/1,000 and <1/100, Rare ≥1/10,000 and <1/1,000, Very rare <1/10,000, Not known (cannot be estimated from the available data). the table describes the various system organ class with their frequency and their respective adverse reactions. These undesirable effects can be described as follows:		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Benylin Wet Cough Menthol syrup	Guaifenesin	Undesirable effects	A. Immune system disorders: very rare-Hypersentivity; B.Nervous system disorders:Not known-Drowsiness; C.Gastrointestinal disorders:Very rare-Diarrhoea, nausea, vomiting, upper abdominal pain,Not known-Gastrointestinal discomfort; Skin and subcutaneous tissue disorders: Very rare-Rash" Addition of text to subtitle to read"Reporting suspected adverse reactions after authorisation of Benylin Wet Cough Menthol is important. It allows continued monitoring of the benefit/risk balance of Benylin Wet Cough Menthol. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8 For further information, please contact the Johnson & Johnson call centre on 0860 410032 (landline)."	27/05/2022	Johnson &Johnson
			Overdose	Revision of text to read"In large doses, guaifenesin will cause drowsiness, nausea and vomiting. It may also cause renal calculi.Treatment is symptomatic and supportive."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	CellCept	Mycophenolate mofetil	Warnings and Precautions	Revision of text under the subtitle Infection to read "Oversuppression of the immune system may also increase susceptibility to infection, including opportunistic infections, fatal infections and sepsis (see “Undesirable effects). In the three controlled studies of rejection prophylaxis after renal transplantation, the incidence of fatal infections was similar in patients receiving CellCept or the control treatment in combination with other immunosuppressants (<2%). In the controlled study on rejection prophylaxis following cardiac transplantation, fatal infections occurred in 1.7% of patients treated with CellCept and 3.8% treated with azathioprine in combination with other immunosuppressants. In cardiac transplant patients treated with CellCept, herpes virus infections (H. simplex, H. zoster and cytomegalovirus [CMV]) were more frequent than in patients receiving azathioprine (see “Undesirable effects). Herpes simplex infections were also more frequent in hepatic patients treated with CellCept than in those treated with azathioprine. Such infections include latent viral reactivation, such as hepatitis B or C reactivation, or infections caused by polyomaviruses Cases of JC virus-associated progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with CellCept. A causal relationship between (PML) and mycophenolate mofetil cannot be clarified because of other factors such as the underlying disease, immunosuppressant comedication and latency period. However, the possibility cannot be excluded that mycophenolate mofetil plays a role. In immunosuppressed patients who develop neurological symptoms, physicians should therefore consider PML in the differential diagnosis.	19/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	CellCept	Mycophenolate mofetil	Warnings and Precautions	BK virus-associated nephropathy has been observed during the use of CellCept in patients post renal transplant.This infection can be associated with serious outcomes, sometimes including renal graft loss. Patient monitoring may help detect patients at risk of BK virus-associated nephropathy. Due to the cytostatic effect of CellCept on B and T lymphocytes, COVID-19 may follow a more severe course. Dose reduction or discontinuation of CellCept should be considered in patients with evidence of BK virus-associated nephropathy or in cases of clinically significant COVID-19."	19/05/2022	Roche
			Interaction	Revision of text under the subtitle Ciprofloxacin and amoxicillin plus clavulanic acid to read "A 54% reduction in pre-dose (trough) MPA concentrations has been reported in renal transplant recipients in the days immediately following administration of oral with ciprofloxacin or amoxicillin plus clavulanic acid. This effect tends to diminish with continued antibiotic use and it ceases after antibiotic withdrawal. It is recommended that MPA exposure be monitored and CellCept doses adjusted to maintain clinical efficacy when coadministering both medicinal products."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	CellCept	Mycophenolate mofetil	Post-marketing experience	Insertion of text under subtitle General disorders and administration site conditions to read"Uncommon: De novo purine synthesis inhibitors-associated acute inflammatory syndrome." Insertion of text under subtitle General disorders and administration site conditions to read"De novo purine synthesis inhibitors-associated acute inflammatory syndrome is a newly described paradoxical pro-inflammatory reaction associated with mycophenolate and other purine synthesis inhibitors and characterised by fever, arthralgia, arthritis, muscle pain and elevated inflammatory markers. According to isolated literature reports, rapid improvement was observed after discontinuation of the drug. 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 via the ElViS (Electronic Vigilance System) online portal. Information can be found at www.swissmedic.ch.."	19/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	CellCept	Mycophenolate mofetil	Pharmacokinetics	Revision of text under subtitle Elimination to read"Approximately 93% of the dose is excreted via the kidneys, mainly as MPAG, and about 5.5% in the faeces. MPAG secreted into the bile undergoes enterohepatic recirculation. Enterohepatic recirculation makes it difficult to determine the t½ of MPA. The apparent half-life is , hence only approximate values can be given. In healthy volunteers and patients with autoimmune disease, clearance values of approximately 10.6 l/h and 8.27 l/h, respectively, and half-lives of 17 h were observed. In transplant patients, mean clearance values were higher (range: 11.9-34.9 l/h) and mean half-lives shorter (5-11 h), with little difference between renal, hepatic and cardiac transplant patients. For each individual patient, these elimination parameters depend, among other things, on the type of any concomitant treatment with other immunosuppressants, time elapsed since transplantation, plasma albumin concentration and renal function. These cofactors may explain why lower exposure is observed when CellCept is coadministered with ciclosporin (see “Warnings and precautions”) and why plasma concentrations tend to increase with time compared to the values observed immediately after transplantation (see “Pharmacokinetics – Absorption”). MPA elimination depends on various transport proteins. Organic anion-transporting polypeptides (OATPs) and multidrug resistance protein 2 (MRP2) are involved in MPA elimination; OATP isoforms, MRP2 and breast cancer resistance protein (BCRP) are transporters associated with biliary excretion of glucuronides. Multidrug resistance protein 1 (MRP1) is also able to transport MPA, but its contribution seems to be confined to the absorption process. In the kidney, MPA and its metabolites interact strongly with renal organic anion transporters."	19/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	CellCept	Mycophenolate mofetil	Other Information	Revision of text under subtitle Incompatibilities to read"CellCept powder for oral suspension must not be mixed with other drugs. CellCept i.v. infusion solution must not be mixed with other intravenous medicines or infusion admixtures or administered concurrently via the same infusion set." Insertion of text under subtitle CellCept film-coated tablets to read "Do not store above 25°C. Store in the original pack in order to protect the contents from light." Insertion of text under subtitle Preparation of the suspension to read"It is recommended that CellCept suspension be prepared by a professional before it is dispensed to the patient. It is recommended that disposable gloves be worn during reconstitution and when wiping the outside of the bottle/lid and table after reconstitution. 1. Shake the closed bottle several times to loosen the powder. 2. Add 94 ml of purified water (aqua purificata) to a measuring cylinder. 3. Pour about half the purified water into the bottle. Then close the bottle and shake carefully for about 1 minute. 4. Add the rest of the water to the bottle and again shake the closed bottle for about 1 minute. 5. Remove the childproof cap and insert the bottle adapter into the neck of the bottle. 6. Reclose the bottle tightly with the childproof cap. This ensures childproof closure of the bottle and correct positioning of the adapter. 7. Write the expiry date of the reconstituted suspension on the bottle label. The reconstituted suspension can be stored for up to 60 days."	19/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Ciloxan	Ciproflaxacin	Indication	Revision of text to read " Ciloxan Eye drops are indicated for the treatment of corneal ulcers and superficial infections of the eye and adnexa caused by ciprofloxacin susceptible strains of bacteria. Ciloxan Eye drops is indicated in adults and pediatric patients including neonates, infants, children and adolescents aged 0 to 18 years."	12/05/2022	Norvatis
			Dosage Regimen and Administration	Revision of text under the heading Dosage regimen to read " Corneal ulcers: Ciloxan Eye drops must be administered in the following intervals, even during night time: • On the first day, instill 2 drops into the affected eye(s) every 15 minutes for the first 6 hours and then 2 drops into the affected eye(s) every 30 minutes for the remainder of the day. • On the second day, instill 2 drops in the affected eye(s) hourly. • On the third through the fourteenth day, place two drops in the affected eye(s) every 4 hours. If the patient needs to be treated longer than 14 days, the dosing regimen is at the discretion of the attending physician. • A maximum duration of therapy of 21 days is recommended. Superficial infections of the eye and adnexa: • The usual dose is one or two drops in the affected eye(s) four times a day. In severe infections, the dosage for the first two days may be one or two drops every two hours during waking hours. • A maximum duration of therapy of 21 days is recommended. The dosage in children above the age of 1 year is the same as for adults. "		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Ciloxan	Ciproflaxacin	Dosage Regimen and Administration	Revision of text under the heading Special populations to read " Renal and hepatic impairment. No studies have been performed in patients with renal or hepatic impairment. Pediatric patients (below 18 years) Ciloxan may be used in pediatric patients at the same dose as in adults. Geriatric patients (65 years or above) No dosage regimen adjustment is required in patients 65 years of age or above. Method of administration • For ocular use only. • After cap is removed, if tamper evident snap collar is loose, it should be removed before using the product. • To avoid contamination, the tip of the dropper / tube should not touch any surface and should also not come into contact with the eye as this may cause injury to the eye. • Either nasolacrimal occlusion or gently closing the eyelid(s) after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions. • Patients should remove contact lenses prior to application and wait at least 15 minutes before reinsertion. If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointment should be administered last."	12/05/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Ciloxan	Ciproflaxacin	Warnings and Precautions	Revision of text to read " • In patients with corneal ulcer and frequent administration of [Ciloxan Eye drops], white topical ocular precipitates (medication residue) have been observed which resolved after continued application of [Ciloxan Eye drops]. The precipitate does not preclude the continued application of [Ciloxan Eye drops], nor does it interfere with antibacterial therapeutic response. However, precipitates may delay epithelial healing." Revision of text under the heading Special excipients to read " Ciloxan Eye drops] contains benzalkonium chloride which may cause eye irritation and may possibly discolor soft contact lenses. Contact lenses, must be removed before administration of [eye drops] and reinserted at least 15 minutes later."	12/05/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Ciloxan	Ciproflaxacin	Adverse Drug Reactions	System organ class Nervous system disorders. Addition of the Frequency category "Common" under the System organ class Eye disorders. Addition of the Frequency category "Uncommon" under the System organ class Eye disorders. Addition of the Frequency category "Rare" under the System organ class Eye disorders. Addition of the Frequency category "Rare" under the System organ class Ear and labyrinth disorders. Addition of the Frequency category "Rare" under the System organ class Respiratory, thoracic and mediastinal disorders. Addition of the Frequency category "Common" under the System organ class Gastrointestinal disorders. Addition of the Frequency category "Uncommon" under the System organ class Gastrointestinal disorders. Addition of the Frequency category "Rare" under the System organ class Gastrointestinal disorders.	12/05/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Ciloxan	Ciproflaxacin	Adverse Drug Reactions	Addition of the Frequency category "Rare" under the System organ class Skin and subcutaneous tissue disorders. Addition of the heading "Adverse drug reactions from spontaneous reports and literature cases (frequency not known)" Revision of text under the heading Adverse drug reactions from spontaneous reports and literature cases (frequency not known) to read " The following adverse drug reactions have been derived from post-marketing experience with Ciloxan via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness." Addition of the subheading " Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)" under the heading Adverse drug reactions from spontaneous reports and literature cases (frequency not known)	12/05/2022	Novartis
			Pregnancy, lactation, females and males of reproductive potential	Deletion of text "Fertility Studies have not been performed in humans to evalaute the effects of topical adminsitration of ciprofloxacin on fertility. Oral admisnitration in animals does not indicate the direct harmful effects with respect to fertility " under this section. Addition of the subheading "Risk summary" under the heading Pregnancy		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Ciloxan	Ciproflaxacin	Pregnancy, lactation, females and males of reproductive potential	Revision of text under the subheading Risk summary to read "It is not known if ciprofloxacin is transferred into human milk following topical ocular administration. Systemically administered ciprofloxacin has been found in human milk. It is not likely that the amount of ciprofloxacin would be detectable in human milk or be capable of producing clinical effects in the infant following topical ocular or otic use of the product. However, a risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman." Addition of the heading "Females and males of reproductive potential" under this section. Revision of subheading to read "Infertility" under the heading Females and males of reproductive potential. Revision of text undr the subheading Infertility to read "There are no data regarding the effects of topical ocular administration of Ciloxan on human fertility. Oral administration in animals does not indicate direct harmful effects with respect to fertility."	12/05/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Ciloxan	Ciproflaxacin	Clinical Pharmacology	Addition of the subheading "Renal impairment" under the heading Pharmacokinetics Addition of text "In patients with impaired renal function, the elimination half-life of ciprofloxacin is only moderately increased due to extrarenal routes of elimination. " under the subheading Renal impairment Addition of the subheading "Hepatic impairment" under the heading Pharmacokinetcs Revision of text under the subheading Hepatic impairment to read "In patients with severely reduced liver function, the elimination half-life is only slightly longer."	12/05/2022	Novartis
8	Glivec	100mg or 400mg imatinib (as mesilate beta crystals)	Adverse drug reactions	Addition of text to read " panniculitis (including erythema nodosum)" under the heading adverse drug reactions from post-marketing reports	28/04/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
9	Hemlibra	Emicizumab 30mg/ml, Emicizumab 150mg/ml	Undesirable effects	Revision of text under the subtitle Summary of the safety profile to read"The overall safety profile of Hemlibra is based on data from clinical trials and post-marketing surveillance. The most serious adverse drug reactions (ADRs) reported from the clinical trials with Hemlibra were thrombotic microangiopathy (TMA) and thrombotic events, including cavernous sinus thrombosis (CST) and superficial vein thrombosis contemporaneous with skin necrosis (see below and section 4.4). The most common ADRs reported in ≥ 10% of patients treated with at least one dose of Hemlibra were: injection site reactions (20 %), arthralgia (15 %) and headache (14 %). In total three patients (0.8 %) in the clinical trials receiving Hemlibra prophylaxis withdrew from treatment due to ADRs, which were TMA, skin necrosis contemporaneous with superficial thrombophlebitis, and headache." Revision of text under the subtitle Tabulated list of adverse drug reactions to read"The following adverse drug reactions (ADRs) are based on data from post-marketing surveillance and pooled data from four phase III clinical trials (adult and adolescent studies [BH29884 -HAVEN 1, BH30071 – HAVEN 3, and BO39182 – HAVEN 4] and a paediatric study BH29992) - HAVEN 2]), in which a total of 373 male patients with haemophilia A received at least one dose of Hemlibra as routine prophylaxis. Two hundred and sixty-six (71 %) of the clinical trial participants were adults. 47(13 %) were adolescents (≥ 12 to < 18 years), 55 (15 %) were children (≥ 2 to < 12 years) and five (1 %) were infants and toddlers (1 month to < 2 years). The median duration of exposure across the studies was 33 weeks (range: 0.1 to 94.3 weeks).	19/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
9	Hemlibra	Emicizumab 30mg/ml, Emicizumab 150mg/ml	Undesirable effects	ADRs from the phase III clinical trials and post-marketing surveillance are listed by MedDRA system organ class (Table 2). The corresponding frequency categories for each ADR are based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). From table 2,The system organ Blood and lymphatic system disorders frequency is common and that for Musculoskeletal and connective tissue disorders is stated as very common." Revision of text under title Description of selected adverse drug reactions with subtitle Thrombotic microangiopathy to read "In pooled phase III clinical trials, thrombotic microangiopathy (TMA) events were reported in less than 1 % of patients (3/373) and in 9.7 % of patients (3/31) who received at least one dose of aPCC while being treated with emicizumab. All 3 TMAs occurred when on average a cumulative amount of > > 100 U/Kg/24 hours of aPCC for 24 hours or more was administered during a treatment event (see section 4.4). Patients presented with thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury, without severe deficiencies in ADAMTS13 activity. One patient resumed Hemlibra following resolution of TMA without recurrence." Revision of text under title Description of selected adverse drug reactions with subtitle Thrombotic events to read"In pooled phase III clinical trials, serious thrombotic events were reported in less than 1% of patients (2/373) and in 6.5% of patients (2/631) who received at least one dose of aPCC while being treated with emicizumab	19/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
8	Hemlibra	Emicizumab 30mg/ml, Emicizumab 150mg/ml	Pharmacological properties	Addition of text under the subtitle Clinical studies in adults and adolescents to read "Patients (aged ≥ 12years old and > 40 kg) with hemophilia A without FVIII inhibitors (Study BH30071 – HAVEN 3). The HAVEN 3 study was a randomized, multicenter, open-label, phase III clinical study in 152 adult and adolescent males (aged ≥ 12 years and > 40 kg) with severe hemophilia A without FVIII inhibitors who previously received either episodic (“on demand”) or prophylactic treatment with FVIII. Patients received subcutaneous Hemlibra, 3 mg/kg once weekly for the first four weeks followed by either 1.5 mg/kg once weekly (Arms A and D) or 3 mg/kg every two weeks (Arm B) thereafter, or no prophylaxis (Arm C). Patients in Arm C could switch to Hemlibra (3 mg/kg every two weeks) after completing at least 24 weeks without prophylaxis. For Arms A and B dose up-titration to 3 mg/kg weekly was allowed after 24 weeks for patients who experienced two or more qualified bleeds (i.e., spontaneous and clinically significant bleeds occurring at steady state). Arm D patients could up-titrate after the second qualifying bleed. At the time of the primary analysis, five patients underwent up-titration of their maintenance dose. Eighty-nine patients previously treated with episodic (“on demand”) FVIII were randomized in a 2:2:1 ratio to receive Hemlibra either once weekly (Arm A; N = 36), every two weeks (Arm B; N = 35) or no prophylaxis (Arm C; N = 18), with stratification by prior 24-week bleed rate (< 9 or ≥ 9). Sixty-three patients previously treated with prophylactic FVIII were enrolled into Arm D to receive Hemlibra (1.5 mg/kg once weekly).The primary objective of the study was to evaluate in patients previously treated with episodic FVIII the efficacy of prophylactic Hemlibra weekly (Arm A) or every two weeks (Arm B) compared to no prophylaxis (Arm C) based on the number of bleeds requiring treatment with coagulation factors (see Table 4).	19/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
8	Hemlibra	Emicizumab 30mg/ml, Emicizumab 150mg/ml	Pharmacological properties	The study also evaluated the efficacy of weekly Hemlibra prophylaxis compared with previous episodic (on-demand) and prophylactic bypassing agents (separate comparisons) in patients who had participated in the NIS prior to enrolment (Arms A and C, respectively see Table 7). In Patients (aged ≥ 12 years old) with haemophilia A with or without factor VIII inhibitors (Study BO39182 – HAVEN 4) Hemlibra was investigated in a single arm, multicenter, phase III clinical study in 41 adult and adolescent males (aged ≥ 12 years and > 40 kg) who have hemophilia A with FVIII inhibitors or severe hemophilia A without FVIII inhibitors who previously received either episodic (“on demand”) or prophylactic treatment with bypassing agents or FVIII. Patients received Hemlibra prophylaxis – 3 mg/kg once weekly for four weeks followed by 6 mg/kg every four weeks thereafter. The primaryobjective of the study was to evaluate the efficacy of Hemlibra prophylaxis given every four weeks in maintaining adequate bleed control, based on treated bleeds. Other objectives were to evaluate the clinical efficacy of Hemlibra prophylaxis on all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds (see Table 8). Patient treatment preference was also assessed using a preference survey."	19/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
9	Invanz	Ertapenem	Special warnings and precautions for use	Revision of text include Under heading Encephalopathy "Encephalopathy has been reported with the use of ertapenem (see section 4.8). If ertapenem-induced encephalopathy is suspected (e.g. myoclonus, seizures, altered mental status, depressed level of consciousness), discontinuation of ertapenem should be considered. Patients with renal impairment are at higher risk of ertapenem-induced encephalopathy and the resolution may be prolonged.''	26/05/2022	MSD
10	Jardiance	Empagliflozin	Interaction with other medicinal products and other forms of interaction	Revision of text to read "Empagliflozin may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after empagliflozin initiation and dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium."Under the heading Effects of empagliflozin on other medicinal products"	14/03/2022	Novartis
			Undesirable effects	Addition of text to read in a tabulated list of adverse reactions in system organ class, Renal and urinary disorders "Tubulo- interstitial nephritis"under the heading very rare.		
			What you need to know before you take Jardiance	Revision of text to read under the heading Do not take Jardiance "•if you are allergic to empagliflozin or any of the other ingredients of this medicine (listed in section 6)."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Jardiance	Empagliflozin	Clinical Particulars	Revision of text to read under the heading therapeutic indication,sub heading Type 2 diabetes mellitus "Jardiance is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise -as monotherapy when metformin is considered inappropriate due to intolerance -in addition to other medicinal products for the treatment of diabetes"	14/03/2022	Novartis
			Posology and method of administration	Revision of text to read under the heading Posology " Type 2 diabetes mellitus The recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other medicinal products for the treatment of diabetes. In patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 ml/min/1.73 m2 and need tighter glycaemic control, the dose can be increased to 25 mg once daily. The maximum daily dose is 25 mg (see below and section 4.4). Heart failure The recommended dose is 10 mg empagliflozin once daily. All indications When empagliflozin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see sections 4.5 and 4.8).		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Jardiance	Empagliflozin	Posology and method of administration	Because the glycaemic lowering efficacy of empagliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe renal impairment, if further glycaemic control is needed, the addition of other anti-hyperglycaemic agents should be considered. For dose adjustment recommendations according to eGFR or CrCL refer to Table 1. Refer to Table 1: Dose adjustment recommendations patients with type 2 diabetes mellitus and established cardiovascular diseaseFor treatment of heart failure in patients with or without type 2 diabetes mellitus, empagliflozin 10 mg may be initiated or continued down to an eGFR of 20 ml/min/1.73 m2 or CrCl of 20 ml/min. Empagliflozin should not used in patients with end stage renal disease (ESRD) or in patients on dialysis. There are insufficient data to support use in these patients (see sections 4.4, 5.1 and 5.2). Hepatic impairment No dose adjustment is required for patients with hepatic impairment. Empagliflozin exposure is increased in patients with severe hepatic impairment. Therapeutic experience in patients with severe hepatic impairment is limited and therefore not recommended for use in this population (see section 5.2).	14/03/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Jardiance	Empagliflozin	Special warnings and precautions for use	Revision of text to read "Ketoacidosis Rare cases of ketoacidosis, including life-threatening and fatal cases, have been reported in patients with diabetes mellitus treated with SGLT2 inhibitors, including empagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/l (250 mg/dl). It is not known if ketoacidosis is more likely to occur with higher doses of empagliflozin. The risk of ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. In patients where ketoacidosis is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately	14/03/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Jardiance	Empagliflozin	Special warnings and precautions for use	Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with empagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised. Before initiating empagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered. Patients who may be at higher risk of ketoacidosis include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients. Restarting SGLT2 inhibitor treatment in patients with previous ketoacidosis while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved. Jardiance should not be used for treatment of patients with type 1 diabetes. Data from a clinical trial program in patients with type 1 diabetes showed increased ketoacidosis occurrence with common frequency in patients treated with empagliflozin 10 mg and 25 mg as an adjunct to insulin compared to placebo.	14/03/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Jardiance	Empagliflozin	Special warnings and precautions for use	For the indication of heart failure, Jardiance is not recommended in patients with eGFR <20 ml/min/1.73 m2. Empagliflozin should not be used in patients with ESRD or in patients on dialysis. There are insufficient data to support use in these patients (see sections 4.2, 5.1 and 5.2). Monitoring of renal function Assessment of renal function is recommended as follows: -Prior to empagliflozin initiation and periodically during treatment, i.e. at least yearly (see sections 4.2, 4.8, 5.1 and 5.2). -Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function. Risk for volume depletion Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying glucosuria may lead to a modest decrease in blood pressure (see section 5.1). Therefore, caution should be exercised in patients for whom an empagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or patients aged 75 years and older. In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with empagliflozin should be considered until the fluid loss is corrected.	14/03/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Jardiance	Empagliflozin	Special warnings and precautions for use	Elderly The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status. Patients aged 75 years and older may be at an increased risk of volume depletion. A higher number of these patients treated with empagliflozin had adverse reactions related to volume depletion as compared to placebo (see section 4.8). Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors). Complicated urinary tract infections Cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin (see section 4.8). Temporary interruption of empagliflozin should be considered in patients with complicated urinary tract infections. Necrotising fasciitis of the perineum (Fournier's gangrene) Cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients with diabetes mellitus taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment. Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier´s gangrene is suspected, Jardiance should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.	14/03/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Jardiance	Empagliflozin	Special warnings and precautions for use	Lower limb amputations An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care. Hepatic injury Cases of hepatic injury have been reported with empagliflozin in clinical trials. A causal relationship between empagliflozin and hepatic injury has not been established. Elevated haematocrit Haematocrit increase was observed with empagliflozin treatment (see section 4.8). Chronic kidney disease There is experience with empagliflozin for the treatment of diabetes in patients with chronic kidney disease (eGFR ≥30 mL/min/1.73 m2) both with and without albuminuria. Patients with albuminuria may benefit more from treatment with empagliflozin. Urine laboratory assessments Due to its mechanism of action, patients taking Jardiance will test positive for glucose in their urine. Interference with 1,5-anhydroglucitol (1,5-AG) assay. Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.	1r4/03/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Jardiance	Empagliflozin	Special warnings and precautions for use	Lactose The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product. Sodium Each tablet contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium free'.	14/03/2022	Novartis
11	Kadcyla	Trastuzumab emtansine	Indications /Uses	Addition of the heading "Early breast cancer (EBC)" under this section Addition of the text "Kadcyla is indicated as monotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual disease in the breast and/or lymph nodes following preoperative taxane-containing chemotherapy in combination with at least trastuzumab as HER2-targeted therapy." under the heading Early breast cancer (EBC)	17/05/2022	Roche
			Dosage /Administration	Addition of the heading "Duration of treatment" under this section Adiition of the text"Patients with EBC should be treated for a total of 14 cycles unless there is disease recurrence or unmanageable toxicity.Patients with MBC should be treated until disease progression or unmanageable toxicity. under the heading Duration of treatment		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Kadcyla	Trastuzumab emtansine	Warnings and precautions	Revision of text under the heading Pulmonary toxicity to read "It is recommended that treatment with Kadcyla be permanently discontinued in patients who are diagnosed with ILD or pneumonitis be permanently discontinued., except for radiation pneumonitis in the adjuvant setting, where Kadcyla should be permanently discontinued if radiation pneumonitis is Grade ≥3 or else Grade 2 that does not respond to standard treatment (see “Dose/Administration, Dose modification”). Patients with dyspnoea at rest due to complications of advanced malignancy, comorbidities and/or receiving concurrent pulmonary radiation therapy may be at increased risk of pulmonary events . Patients with interstitial lung disease or pneumonitis should not be started on treatment with Kadcyla"	17/05/2022	Roche
			Undesirable effects	Revision of text under heading Eye disorders to read"Common: Dry eye (5.3%), lacrimation increased (4.5%), vision blurred 3.9%, conjunctivitis (3.7%)." Revision of text under the heading Cardiac disorders to read"Common: Left ventricular dysfunction (2.5%; ≥Grade 3: 0.4%)." Revision of text under the heading Vascular disorders to read " Very common: Haemorrhage (33.2%; ≥Grade 3: 1.7%). Common: Hypertension (6.2%; ≥Grade 3: 1.8%). " Revision of text under the heading Respiratory, thoracic and mediastinal disorders to read " Very common: Epistaxis (23.5%; ≥Grade 3: 0.3%), cough (17.8%; ≥Grade 3: 0.1%), dyspnoea (12.0%; ≥Grade 3: 1.1%).Uncommon: Pneumonitis (0.8%; ≥Grade 3: 0.1%)."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Kadcyla	Trastuzumab emtansine	Undesirable effects	Revision of text under the heading Skin and subcutaneous tissue disorders to read "Common: Rash (12.49.2%; ≥Grade 3: 0.3%). Common: Pruritus2%), pruritus (6.0%; ≥Grade 3: <0.3%), alopecia (3.4%), nail disorder (2.3%), palmar- plantar erythrodysaesthesia syndrome (1.6%), urticaria (1.1%). Rare: Severe skin reactions (0.2%)." Revision of text under the heading Musculoskeletal and connective tissue disorders to read " Very common: Musculoskeletal pain (34.1%; ≥Grade 3: 1.9%), arthralgia (20.9%; ≥Grade 3: 0.5%), myalgia (13.6%; ≥Grade 3: 0.3%)." Revision of text under the heading General disorders and administration site conditions to read " Very common: Fatigue (40.4%; ≥Grade 3: 2.1%), pyrexia (19.5%; ≥Grade 3: 0.2%), asthenia (11.8%; ≥Grade 3: 0.8%). Common: Chills (8.9%), peripheral oedema (6.9%; ≥Grade 3: 0.1%).Uncommon: Injection site extravasation (0.3%). " Revision of text under the heading Note to read " 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 via the ElViS (Electronic Vigilance System) online portal. Information can be found at www.swissmedic.ch."	17/05/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
12	Lyrica	Pregabalin	Special warnings and precautions for use	Addition of text to read " Pregabalin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus. Women of childbearing potential must use effective contraception during treatment (see Section 4.6 Fertility, pregnancy and lactation)" under the subheading women of childbearing potential/Contraception	09/05/2022	Pfizer
13	MabThera SC	Rituximab SC	Fertility, pregnancy and lactation	Revision of text under the heading Breast-feeding to read " Limited data on rituximab excretion into breast milk suggest very low milk levels (relative infant dose less than 0.4%). Few cases of follow-up of breastfed infants describe normal growth and development up to 1.5 years. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women as these data are limited and the long-term outcomes of breastfed infants remain unknown, breastfeeding is not recommended while being treated with MabThera rituximab and optimally for 12 months following rituximab treatment."	17/05/2022	Roche
14	MabThera IV	Rituximab IV	Dosage / Administration	Revision of text under the the heading ANCA-associated vasculitis (GPA/MPA) in adults to read " Treatment should only be conducted by physicians experienced in the treatment of rheumatic and immunological diseases.In patients with ANCA-associated vasculitis, Pneumocystis jirovecii pneumonia (PCP) prophylaxis is recommended as needed during and after MabThera treatment."	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
14	MabThera IV	Rituximab IV	Dosage / Administration	Addition of text to read "Following induction of remission with MabThera, maintenance treatment in adult patients with GPA and MPA may be initiated no sooner than 16 weeks after the last MabThera infusion. MabThera maintenance treatment should be initiated within 4 weeks of disease remission. Any concomitant corticosteroid therapy should be tapered according to clinical judgment. MabThera should be administered as two 500 mg intravenous infusions two weeks apart, followed by one 500 mg intravenous infusion after 6, 12 and 18 months, then every 6 months as required based on clinical assessment." under the heading Adult maintenance treatment Addition of text to read " The recommended dosage of MabThera for the treatment of pemphigus vulgaris is 1000 mg by intravenous infusion followed two weeks later by a second 1000 mg intravenous infusion in combination with tapering glucocorticoid therapy. Pneumocystis jirovecii pneumonia (PCP) prophylaxis according to local clinical guidelines is recommended for adult patients with PV during and following MabThera treatment, if required prophylaxis is recommended as needed during and after MabThera treatment. A 500 mg intravenous maintenance infusion should be administered after 12 and 18 months, then every 6 months as required based on clinical assessment. Corticosteroids should be tapered according to local guidelines and the physician's clinical judgment.	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
14	MabThera IV	Rituximab IV	Dosage / Administration	Treatment of relapseIn the event of relapse, patients may receive 1000 mg intravenously. The healthcare provider should also consider resuming or increasing the patient's glucocorticoid dose based on clinical evaluation.Subsequent infusions may be administered no sooner than 16 weeks following the previous infusion." under the heading Pemphigus vulgaris (PV) in adults Addition of text to read "Premedication The safety and efficacy of MabThera in paediatric patients ≥6 months to <18 years of age have not been established in indications other than previously untreated advanced CD20-positive DLBCL/BL/BAL/BLL. Clinical data on children under 3 years of age are available from only one patient. The dosage recommendations for children 6 months to 3 years of age are based on simulated pharmacokinetic data from a population PK model (see "Warnings and precautions", "Undesirable effects" and "Pharmacokinetics").MabThera should not be used in paediatric patients <6 months of age with CD20-positive diffuse large B-cell lymphoma (see "Clinical efficacy" "CD20+ DLBCL/BL/BAL/BLL in paediatric patients"). In paediatric patients ≥6 months to <18 years of age with previously untreated advanced CD20- positive DLBCL/BL/BAL/BLL, MabThera should be used in combination with systemic Lymphome Malin B (LMB) chemotherapy (see Tables 1 and 2). The recommended dose of MabThera is 375 mg/m² body surface area, administered as an intravenous infusion. No MabThera dose adjustments other than by body surface area are required. " under the heading Non-Hodgkin's lymphoma	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
14	MabThera IV	Rituximab IV	Dosage / Administration	Induction of remission The recommended dosage of MabThera for remission-induction therapy in paediatric patients with severe active GPA or MPA is 375 mg/m² body surface area, administered as an i.v. infusion once weekly for 4 weeks. MabThera should not be used in paediatric patients less than 2 years of age with severe active GPA or MPA as thereis a possibility of an inadequate immune response to childhood vaccinations against common, vaccine-preventable childhood diseases (e.g. measles, mumps, rubella and poliomyelitis) (see “Clinical efficacy” “Severe active ANCA-associated vasculitis [granulomatosis with polyangiitis (GPA) (Wegener’s granulomatosis) and microscopic polyangiitis (MPA)] in paediatric patients”)."	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
14	MabThera IV	Rituximab IV	Warnings and precautions	Revision of text under the subheading Preventive vaccinations to read"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. It is recommended that, if possible, all immunisations should be updated in line with current guidelines before starting treatment with MabThera." Addition of the subheading "Paediatric patients" under this section. Addition of text to read "Only limited data are available for patients under 3 years of age. For further information, see “Clinical efficacy” “CD20+ DLBCL/BL/BAL/BLL in paediatric patients”. Non-Hodgkin’s lymphoma in children 6 months to <3 years of age In children aged 6 months to <3 years who were receiving treatment with rituximab (n=6), there were three cases of grade 4 sepsis and one of grade 4 Stevens-Johnson syndrome. In addition, all 6 patients had a serious event, including sepsis, Stevens-Johnson syndrome and tumour lysis syndrome."under the subheading Paediatric patients.	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
14	MabThera IV	Rituximab IV	Pregnancy, lactation	Revision of text under the heading Pregnancy 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. Animal studies have shown no reproductive toxicity, although B cell-depleted populations have been exposed to MabThera during pregnancy.found among neonates (see “Preclinical data”). 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." Revision of text under the heading Lactation to read " It is not known whether rituximab is excreted in human milk. Given, however, that maternal IgG enters breast milk and animal studies have shown that rituximab is excreted into milk ,(see “Preclinical data”), women who are being treated with MabThera should not breastfeed." Addition of the subheading Fertility under this section. Addition of text to read "No clinical data are available on fertility with rituximab. Animal studies have revealed no evidence of impaired fertility with rituximab (see “Preclinical data”)." under the subheading Fertility	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
14	MabThera IV	Rituximab IV	Undesirable effects	Revision of text under the heading Experience from clinical studies in adults with NHL and CLL to read " Summary of the safety profile The overall safety profile of MabThera in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated with MabThera either as monotherapy (in the form of induction therapy or maintenance therapy following induction therapy) or in combination with chemotherapy The most frequently observed adverse reactions (ADRs) in patients receiving MabThera were IRRs, which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and was less than 1% after the eighth administration of MabThera. In clinical trials, infections (predominantly bacterial and viral infections) occurred in approximately 30- 55% of patients with NHL and in 30-50% of patients with CLL. The most frequently reported or observed serious adverse reactions were: • IRRs (including cytokine release syndrome, tumour lysis syndrome), see "Warnings and precautions". • Infections, see "Warnings and precautions". • Cardiovascular events, see "Warnings and precautions". Other serious ADRs reported include hepatitis B reactivation and PML (see "Warnings and precautions").	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
14	MabThera IV	Rituximab IV	Undesirable effects	The adverse drug reactions of all degrees of severity listed below are based on data from studies with approximately 2300 adults and 309 paediatric patients in whom MabThera was administered either as monotherapy/maintenance therapy or in combination with chemotherapy. Within each frequency category, adverse drug reactions are listed in decreasing order of severity. 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). The ADRs identified only during post-marketing surveillance, and for which a frequency could not therefore be calculated, are listed under “not known”. Revision of text under the heading Immune system disorders to read "Very common: infusion-related reactions4, angioedema, decreased IgG levels. Common: hypersensitivity. Rare: anaphylaxis. Very rare: tumour lysis syndrome, cytokine release syndrome4, serum sickness Not known: infusion-related acute reversible thrombocytopenia4."	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
14	MabThera IV	Rituximab IV	Undesirable effects	Revision of text under the heading Vascular disorders to read "Common: hypertension, orthostatic hypotension, hypotension. Revision of text under the heading Respiratory, thoracic and mediastinal disorders to read "Common: bronchospasm4, respiratory disease, chest pain, dyspnoea, increased cough, rhinitis. Uncommon: asthma, bronchiolitis obliterans, respiratory failurelung disorder, hypoxia. Rare: pulmonary oedema, interstitial lung disease7. Very rare: respiratory failure4. Not known: pulmonary infiltrates" Revision of text under the heading Skin and subcutaneous tissue disorders to read " Very common: pruritus rash, +alopecia Common: urticaria sweating, night sweats, +skin disorder Very rare: severe bullous skin reactions Stevens-Johnson syndrome, toxic epidermal necrolysis Lyell's syndrome)7." Revision of text under the subheading Overdose to read "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. In the post-marketing setting, five cases of MabThera overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of 1.8 g of rituximab and fatal respiratory failure, with a dose of 2 g of rituximab."	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
15	Mirena Intrauterine Delivery System	Levonorgestrel	Special warnings and precautions for use	Revision of text under subtitle Expulsion to read"Mirena can be expelled from the uterine cavity without the patient noticing it, leading to loss of contraceptive protection. Possible symptoms of partial or complete expulsion of the system may include bleeding and pain. Partial expulsion may decrease the effectiveness of Mirena. As Mirena normally decreases menstrual flow, an increase in menstrual flow may be indicative of an expulsion. A displaced Mirena should be removed. A new system can be inserted at the same time. The woman should be advised on how to check the threads of Mirena in her vagina" Revision of text under the subtitle Perforation to read"Perforation or penetration of the uterine corpus or cervix by an intrauterine contraceptive may occur, most often during insertion, and it may not be detected until later. A system located outside the uterus has reduced contraceptive efficacy: Such a system must be removed. Surgery may be required."	28/04/2022	Bayer

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
16	Micera	Methoxy polyethylene glycol-epoetin beta	Dosage and administration/Administration	Addition of the text " To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment." under the heading Switching from erythropoiesis- stimulating agent (ESA) treatment to Mircera. Addition of the text "In clinical studies, 24% of patients treated with Mircera were 65 to 74 years old and 20% were 75 years or older. No dose adjustment is necessary in patients aged ≥65 years." under the subheading Elderly patients. Addition of the subheading "Delayed administration " under the heading Special dosage instructions. Addition of the text "If a dose of Mircera is missed, the missed dose should be administered as soon as possible and treatment with Mircera continued at the prescribed dosing frequency. " under the subheading delayed adminsitration	17/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
16	Micera	Methoxy polyethylene glycol-epoetin beta	Undersirable effects	Addition of text "The Mircera safety data from clinical trials are based on 3042 CKD patients, including 1939 patients treated with Mircera and 1103 with another ESA. Undesirable effects must be expected in some 6% of patients treated with Mircera. The most frequent reported undesirable effect was hypertension (common)."under this section Addition of text "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 via the ElViS (Electronic Vigilance System) online portal. Information can be found at www.swissmedic.ch."	17/05/2022	Roche
			Undersirable effects	Revision of text under the heading Undesirable effects after market launch to read "Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), skin exfoliation and erythema multiforme, have been reported with Mircera in the post-marketing setting (see “Warnings and precautions”). Frequencies are not known. The occurrence of neutralising anti-erythropoietin antibody-mediated pure red cell aplasia (AEAB- PRCA) has been reported in association with Mircera therapy during post-marketing experience (see “Warnings and precautions”)."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
16	Micera	Methoxy polyethylene glycol-epoetin beta	Overdose	Deletion of the text "The safety profile in the paediatric population was consistent with that in adults.Post-marketing phase Neutralizing antierythropoietin antibody-mediated pure red cell aplasia (AEAB-PRCA) associated with MIRCERA therapy has been reported during post-marketing experience (see Warnings and precautions). Stevens-Johnson syndrome/toxic epidermal necrolysis has been reported." under this section	17/05/2022	Roche
17	Ocrevus	Ocrelizumab	Warnings and precautions	Addition of text to read "Cases of late-onset neutropenia have been reported. Although some cases were grade 3 or 4, the majority of the cases were grade 1 or 2. Cases of late-onset neutropenia have been reported at least 4 weeks after the last Ocrevus infusion. In patients with signs and symptoms of infection, measurement of blood neutrophils is recommended (see “Undesirable effects”)." under the subheading Late neutropenia.	17/05/2022	Roche
			Undesirable effects	Revision of text under this section to read "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 via the ElViS (Electronic Vigilance System) online portal. Information can be found at www.swissmedic.ch. "		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
18	Nimenrix	Neisseria meningitidis group A,C,Y and W-135 polysaccharide	Long term immunogenicity in toddlers	Revision of text to read "Study MenACWY-TT-104 evaluated the immunogenicity after 1 month and the persistence of the response up to 5 years following 1 or 2 doses (given 2 months apart) of Nimenrix in toddlers aged 12 to 14 months. One month following one or two doses administered 2 months apart Nimenrix elicited rSBA titres against all four meningococcal groups that were similar in terms of the percentage of subjects with rSBA titre ≥8 and GMT. As a secondary endpoint hSBA titres were measured. In terms of the percentage of subjects with hSBA titres ≥8, at 1 month post vaccination, hSBA titres against groups W-135 and Y were higher after two doses of Nimenrix than after one dose, while the hSBA titres against groups A and C were similar in the two dose groups. At 5 years post vaccination, the immune response for all four meningococcal groups were similar in both the one and two dose groups for both rSBA and hSBA titres ≥8 (Table 6)"	27/04/2022	Pfizer
			Undesirable effects	Addition of text to read "rash, urticaria" under the heading adverse reactions of skin and subcutaneous tissue disorders.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
19	Perjeta	Pertuzumab	Dosage / Administration	Revision of text under this section to read "It is essential that Perjeta therapy be initiated under the supervision of a physician experienced in the treatment of cancer patients.Tumour status in patients treated with Perjeta should be HER2-positive, defined as an immunohistochemistry (IHC) score of 3+ or an in situ hybridisation (ISH) amplification ratiorate of ≥2.0 determined using a validated test. Perjeta should be administered as an intravenous infusion and not as an intravenous bolus injection. To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment." Revision of text under the heading Metastatic and early breast cancer to read " The recommended initial dose of Perjeta is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by a dose of 420 mg administered over 30 to 60 minutes. A 30- to 60-minute observation period is recommended after each Perjeta infusion." Revision of text under the heading Combination therapy to read " Combination therapy The observation period should be completed prior to any subsequent infusion of Herceptin is or chemotherapy (see “Warnings and precautions”).Perjeta and Herceptin should be administered sequentially in any order.Herceptin is administered as an intravenous infusion at an initial dose of 8 mg/kg, followed by a dose of 6 mg/kg every 3 weeks. In patients treated with a taxane, Perjeta and Herceptin should be administered before the taxane. The recommended initial dose of docetaxel in combination with Perjeta and Herceptin is 75 mg/m2. If this is well tolerated, the dose may be increased to 100 mg/m2.	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
19	Perjeta	Pertuzumab	Interaction	Revision of text under this section to read " Studies have investigated the effect of pertuzumab on the pharmacokinetics of the coadministered cytotoxics trastuzumab, docetaxel, paclitaxel, gemcitabine, erlotinib , carboplatin and capecitabine. There was no evidence of pharmacokinetic interaction between pertuzumab and any of these agents."	26/05/2022	Roche
			Warnings and precautions	Revision of text under the heading Left ventricular dysfunction to read " Decreases in left ventricular ejection fraction (LVEF) have been reported with medicinal products that inhibit HER2 activity, including Perjeta. Patients who have received prior anthracyclines or prior radiotherapy to the chest area are at higher risk of decreased LVEF.a decreased LVEF. The majority of cases of symptomatic heart failure in the adjuvant setting were in patients who had received anthracycline-based chemotherapy (see “Undesirable effects”).Perjeta has not been studied in patients with a pretreatment LVEF value of ≤50%, a prior history of congestive heart failure (CHF), decreases in LVEF to <50% during prior adjuvant Herceptin therapy or conditions that could impair left ventricular function (such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or prior anthracycline exposure to >360 mg/m2 doxorubicin or its equivalent) In patients receiving neoadjuvant treatment, the incidence of left ventricular systolic dysfunction (LVSD) in the Perjeta-treated groups was higher than in the group treated with Herceptin and docetaxel.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
19	Perjeta	Pertuzumab	Warnings and precautions	An increased incidence of declines in LVEF was observed in patients treated with Perjeta in combination with Herceptin and docetaxel; LVEF returned to normal (≥50%) in all patients. The overall incidence of symptomatic declines in LVSD and LVEF in the neoadjuvant phase of the clinical trials was consistent (see “Undesirable effects, Further data on selected adverse effects, Left ventricular dysfunction”).For dose recommendations for LVSD, see Table 1 under “Dosage/Administration”.Infusion-related reactions, hypersensitivity reactions/anaphylaxis. Infusion-related reactions (any event reported as hypersensitivity, anaphylactic reaction, acute infusion reaction or cytokine release syndrome occurring during an infusion or on the day of an infusion), including fatal events, have been reported during treatment with Perjeta (see “Undesirable effects”).Severe hypersensitivity reactions, including anaphylaxis and fatal events, have been observed in patients treated with Perjeta. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Perjeta is contraindicated in patients with known hypersensitivity to pertuzumab or any of the excipients. When administering Perjeta, close patient observation is recommended during and for 60 minutes after the first infusion and during and for 30 minutes after subsequent Perjeta infusions. If the patient develops an infusion-related reaction, the infusion of Perjeta should be slowed or the administration interrupted.	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
19	Perjeta	Pertuzumab	Effects on ability to drive and use machines	Revision of text under this section to read " No relevant studies have been performed. However, nausea, fatigue, vomiting and dizziness have been observed during treatment with Perjeta (see “Undesirable effects on the ability to drive”). Should these symptoms occur, caution is required when driving or operateusing machines"	26/05/2022	Roche
			Pregnancy lactation	Revison of text under the heading Pregnancy to read " Perjeta should not be used during pregnancy except unless the potential benefit for the mother outweighs the possible risk to the fetus. Women of childbearing age and male patients’ female partners of childbearing age should use a reliable method of contraception during treatment with Perjeta and for 6 months after the last dose. No studies have been conducted with Perjeta in pregnant women. Perjeta administered to cynomolgus monkeys during organogenesis caused oligohydramnios, delayed renal development embryo-fetal death (see “Preclinical data”). Based on the animal studies and the mechanism of action, it must be assumed that Perjeta may be harmful to the unborn child if it is administered to a pregnant woman."		
			Undesirable effects	Addition of the text "For the incidences of LVSD and symptomatic LVSD in TRYPHAENA (BO22280), see“Properties/Effects, Clinical efficacy, Study BO22280”.In the neoadjuvant phase of BERENICE, the incidence of symptomatic LVSD (NYHA class III/IV congestive heart failure according to NCI-CTCAE v.4) in the group treated with dose-dense AC	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
19	Perjeta	Pertuzumab	Undesirable effects	Asymptomatic or mildly symptomatic (NYHA class II) declines in LVEF by at least 10% from baseline and to <50% were reported in 2.7% of Perjeta-treated patients and 2.8% of patients in the placebo group, of whom 79.4% and 80.6%, respectively, had recovered at the data cutoff. " under the heading Left ventricular dysfunction Addition of text to read " In neoadjuvant and adjuvant trials, Perjeta was administered on the same day as the other study medications. Infusion-related reactions occurred in 18.6%-25.0% of patients on the first day of Perjeta administration (in combination with Herceptin and chemotherapy). The type and severity of events were consistent with those observed in CLEOPATRA, with the majority of reactions being mild or moderate. In APHINITY, infusion-related reactions occurred in 21% of patients on the first day of Perjeta administration (in combination with trastuzumab and chemotherapy) and in 18% of patients in the placebo arm. The incidence of grade 3-4 reactions was 1% in the Perjeta arm and 0.7% in the placebo arm."under the heading Infusion-related reactions and hypersensitivity reactions	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
19	Perjeta	Pertuzumab	Undesirable effects	Addition of the heading "Diarrhoea" under this section. Addition of the text "In the pivotal trial CLEOPATRA in metastatic breast cancer, rash occurred in 51.7% of Perjeta-treated patients compared to 38.9% of placebo-treated patients. Most cases were grade 1 or 2 in severity, occurred in the first two cycles and responded to standard treatment, such as topical or oral acne therapy. In NEOSPHERE, rash occurred in 40.2% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel compared to 29.0% of patients treated with trastuzumab and docetaxel. In TRYPHAENA, rash occurred in 36.8% of patients treated with neoadjuvant Perjeta + TCH and 20.0% of patients treated with FEC followed by neoadjuvant Perjeta, trastuzumab and docetaxel. The incidence of rash in patients who received six cycles of Perjeta was higher than in patients who received three cycles of Perjeta, regardless of the chemotherapy given. In APHINITY, rash occurred as an adverse reaction in 25.8% of patients in the Perjeta arm vs 20.3% of patients in the placebo arm. The majority of rash events were grade 1 or 2 in severity" under the heading Rash.	26/05/2022	Roche
20	Recormon	Epoetin beta (recombinant human erythropoietin)	Undesirable effects	Revision of text include '' Epoetin beta treatment-related headache and hypertension which can be treated with drugs, has been reported in 1 - 10% of cases (see “Warnings). '' Under heading Cancer patients	23/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
20	Recormon	Epoetin beta (recombinant human erythropoietin)	Instructions for handling	Deletion of text under the heading special instruction for Adminstration '' Epoetin beta is present in the vial as a powder. The contents of the vial are dissolved in the supplied solvent. The powder can alternatively be dissolved in up to 100 ml physiological saline using an infusion bag. Only solutions which are clear or slightly opalescent, colorless and free of visible particles may be injected.''	23/05/2022	Roche
21	Rocephin	Ceftriaxone	Contraindications	Revision of text to read "Treatment of hyperbilirubinaemic neonates is not therefore indicated (see “Contraindications”). "	18/05/2022	Roche
			Warnings and precautions	Revision of text to read "Encephalopathy has been reported with the use of ceftriaxone (see “Undesirable effects”), particularly in elderly patients with severe renal impairment (see “Dosage/Administration”) or central nervous system disorders. If ceftriaxone-associated encephalopathy is suspected (e.g. decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of ceftriaxone should be considered."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
21	Rocephin	Ceftriaxone	Undesirable effects	Revision of text to read under the heading General disorders and administration site condition , Uncommon "injection site pain,reactions (e.g. injection site pain, erythema, warmth, redness, phlebitis, extravasation, swelling, rash, pruritus, inflammation, induration, haematoma, infection, abscess) are asked to report any suspected new or serious adverse reaction via the ElViS (Electronic Vigilance System) online portal. Information can be found at www.swissmedic.ch."	18/05/2022	Roche
			Pharmacokinetics	Revision of text to read "In patients with both severe renal and hepatic dysfunction, clinical monitoring of safety and efficacy is advised."Under the heading Patients with severe renal and hepatic impairment		
			Other information	Delation of text to read "hydroxyethyl starch 6" Under the Heading Intravenous infusion		
22	Ryverna	Crizanlizumab	Pharmacokinetics (PK)	Revision of text to read "Crizanlizumab is administered intravenously. The median time to reach maximum serum concentration of crizanlizumab (Tmax) was 1.92 hours at steady state following an intravenous administration of 5 mg/kg over a period of 30 minutes in sickle cell disease patients."Under the subheading Absorption Revision of text to read under the subheading Eliminartion "In healthy volunteers, the mean terminal elimination half-life (T1/2) was 10.6 days and the mean clearance was 11.7 mL/hr at crizanlizumab dose level 5 mg/kg. In patients with sickle cell disease, the mean elimination T1/2 during dosing interval was 7.611.2 days.	12/05/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
22	Ryverna	Crizanlizumab	Pharmacokinetics (PK)	There was no indication of accelerated clearance or time-dependent change in the pharmacokinetic properties of crizanlizumab following repeated administration."	12/05/2022	Novartis
23	Tamin	Paracetamol	Special warnings and precautions for use	Addition of text to read "Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended." under the heading Warning	31/05/2022	Baxtrer
			Interaction with other medicinal products and other forms of interaction	Addition of text to read "Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors (see section 4.4)" under this section		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
24	Tacrolimus	Tacrolimus	Warnings and precautions	Addition of text to read " •Tacrolimus can result in renal function impairment in post-transplant patients. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced. The risk for nephrotoxicity may increase when tacrolimus is concomitantly administered with drugs associated with nephrotoxicity. Concurrent use of tacrolimus with drugs known to have nephrotoxic effects should be avoided. When co-administration cannot be avoided, tacrolimus trough blood level and renal function should be monitored closely, and dosage reduction should be considered if nephrotoxicity occurs."	15/06/2022	Novartis
			Other medicines and Tacrolimus Sandoz	Addition of text to include "Concomitant use of medicinal products or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. " Addition of text to include " • the CMV antiviral letermovir, the pharmacokinetic enhancer cobicistat, and the tyrosine kinase inhibitors nilotinib and imatinib. Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients. • Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided. • Care should be taken when tacrolimus is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole)		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
24	Tacrolimus	Tacrolimus	Possible side effects	Addition of text to read " • Opportunistic infections (bacterial, fungal, viral, and protozoal) like CMV infection, BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions including graft rejection that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating hepatic or renal function or neurological symptoms: prolonged diarrhea, fever, and sore throat. Benign and malignant tumours have been reported following treatment as a result of immunosuppression. Patients are also at risk for viral hepatitis from either reactivation or new infections from hepatitis B, C and E which may be chronic and de novo infection. • Patients receiving immunosuppressive therapy are at increased risk of developing malignancies Addition of text to read " • Anemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal." Under the heading Common side effects (may affect up to 1 in 10 people).	15/06/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
25	Tecentriq	Atezolizumab	Special warnings and precautions for use	Deletion of subheading "infusion related reaction". Addition of text "Given the mechanism of action of atezolizumab, other potential immune-related adverse reactions may occur, including noninfective cystitis.	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
25	Tecentriq	Atezolizumab	Special warnings and precautions for use	Addition 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 the subheading "disease specific precautions". Addition of text "Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin 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. 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.	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
25	Tecentriq	Atezolizumab	Special warnings and precautions for use	Revision of text to read "22.1+ months; + denotes a censored value). SCARs led to discontinuation of atezolizumab in 3 (< 0.1%) patients. SCARs requiring the use of systemic corticosteroids occurred in 0.2% (8/3 854) of patients receiving atezolizumab monotherapy. Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin. In the usefirst-line NSCLC study (IMpower150), an overall higher frequency of systemic corticosteroids occurredadverse events was observed in 0.2% (8/3,854)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 monotherapyin 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 subheading "Immune-related severe cutaneous adverse reactions".	26/05/2022	Roche

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
25	Tecentriq	Atezolizumab	Special warnings and precautions for use	Addition of text "In study IMpower150, age ≥ 65 was associated with an increased risk of developing adverse events in patients receiving atezolizumab in combination with bevacizumab, carboplatin and paclitaxel. In studies IMpower150, IMpower133 and IMpower110, data for patients ≥ 75 years of age are too limited to draw conclusions on this population.	26/05/2022	Roche
			Shelf life	Addition of text "unopened vial" and "3years" under the heading "shelf life".		
			Special precautions for disposal and other handling	Revision of text to read "For the recommended dose of 1 200 mg: twenty 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" under the subheading "instructions for dilution".		
26	Xeloda	Capecitabine	Undesirable effects	Addition of text "Frequency not known: angioedema (observed in the post-marketing setting)" under the subheading "hypersensitivity reactions".	27/05/2022	Roche
			Shelf life	Addition of text "Keep the container in the outer carton in order to protect the contents from moisture" under the subheading "shelf life".		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH