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	Amlodipine/ Indapamide	Natrixam	Special warnings and precautions for use	Revision of text under the subheading Plasma postassium to read "Potassium depletion with hypokalaemia is the major risk of thiazide and related diuretics. Hypokalaemia may cause muscle disorders. Cases of Rhabdomyolysis have been reported, mainly in the context of severe hypokalaemia. The risk of onset of hypokalaemia (< 3.4 mmol/l) must be prevented in certain high risk populations, i.e. the elderly, malnourished and/or polymedicated, cirrhotic patients with oedema and ascites, coronary artery disease and cardiac failure patients. In this situation, hypokalaemia increases the cardiac toxicity of digitalis preparations and the risks of arrhythmias.Individuals with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as well as bradycardia, is then a predisposing factor to the onset of severe arrhythmias, in particular, potentially fatal torsades de pointes. More frequent monitoring of plasma potassium is required in all the situations indicated above. The first measurement of plasma potassium should be obtained during the first week following the start of treatment.Detection of hypokalaemia requires its correction. Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected." Addition of the subheading "Plasma magnesium" under the heading Precautions for use Addition of the text "Thiazides and related diuretics including indapamide have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see section 4.5 and 4.8)." under the subheading Plasma magnesium	17/08/2022	Les Lobaratoires Servier
			Interaction with other medicinal products and other forms of interaction	Revision of text under the heading Digitalis to read "Hypokalaemia and/or hypomagnesaemia predispose to the toxic effects of digitalis. Monitoring of plasma potassium and magnesium and ECG is recommended and, if necessary,review the treatment."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	Amlodipine / Indapamide	Natrixam	Undesirable effects	Deletion of the text "During clinical studies, hypokalaemia (plasma potassium < 3.4 mmol/l) was seen in 10 % of patients and < 3.2 mmol/l in 4 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/l. (see section 4.4)." under the adverse reaction Hypokalemia of the Medra System organ class Metabolism and nutrition disorders Addition of the adverse reaction Hypochloraemia under the MedDRA System organ class Metabolism and nutrition disorders. Addition of the requency "Rare" under the adverse reaction Hypochloraemia of the MedDRA System organ class Metabolism and nutrition disorders. Addition of the adverse reaction "Hypomagnesaemia" under the MedDRA System organ class Metabolism and nutrition disorders. Addition of the requency "Rare" under the adverse reaction Hypomagnesaemia of the MedDRA System organ class Metabolism and nutrition disorders. Addition of the heading Description of selected adverse reactions under this section Addition of the text "During phase II and III studies comparing indapamide 1.5 mg and 2.5 mg, plasma potassium analysis showed a dose-dependent effect of indapamide: - Indapamide 1.5 mg: Plasma potassium < 3.4 mmol/l was seen in 10 % of patients and < 3.2 mmol/l in 4 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean decrease in plasma potassium was 0.23 mmol/l. - Indapamide 2.5 mg: Plasma potassium < 3.4 mmol/l was seen in 25 % of patients and < 3.2 mmol/l in 10 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean decrease in plasma potassium was 0.23 mmol/l. - Indapamide 2.5 mg: Plasma potassium < 3.4 mmol/l was seen in 25 % of patients and < 3.2 mmol/l in 10 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean decrease in plasma potassium was 0.41 mmol/l." under the heading Description of selected adverse reactions	17/08/2022	Les Lobaratoires Servier

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Augmentin 228.5mg& 457mg suspension	Amoxicillin/ Clavulanic acid suspension(228.5mg/457mg)	Special warnings and precautions for use	Revision of text to read"Before initiating therapy with Augmentin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity (see Contraindications). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to Augmentin (see Undesirable effects). If an allergic reaction occurs, Augmentin therapy must be discontinued, and appropriate alternative therapy instituted. Serious anaphylactic reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous (i.v.) steroids and airway management (including intubation) may also be required. Augmentin should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin. Prolonged use may also occasionally result in overgrowth of non-susceptible organisms. Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately, and the patient investigated further. Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving Augmentin and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation. Changes in liver function tests have been observed in some patients receiving Augmentin. The clinical significance of these changes is uncertain, but Augmentin should be used with caution in patients with evidence of hepatic dysfunction. Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for up to six weeks after treatment has ceased. In patients with renal impairment Augmentin suspension 228 mg/5 ml and 457 mg/5 ml are not recommended. In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see Overdose). Augmentin 228 mg/5 ml and 457 mg/5ml suspensions contain aspartame, which is a source of phenylalanine and so should be used with cautiontaken in patients with phenylketonuria."	16/08/2022	GlaxoSmithKline Export Limited

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Augmentin 228.5mg& 457mg suspension	Amoxicillin/ Clavulanic acid suspension(228.5mg/457mg)	Interaction with other medicinal products and other forms of interaction	Revision of text to read"Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with Augmentin may result in increased and prolonged blood levels of amoxicillin but not of clavulanateclavulanic acid. Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of Augmentin and allopurinol. In common with other antibiotics, Augmentin may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.	16/08/2022	GlaxoSmithKline Export Limited
			Interaction with other medicinal products and other forms of interaction	In the literature there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If coadministration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of Augmentin. In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure."		
			Undesirable effects	Insertion of text under subtitle Cardiac disorders to read"Very rare Kounis syndrome (see Special warnings and precautions for use). "		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Augmentin 625mg, 1g tablet	Amoxicillin/ Clavulanic acid 625mg /1g tablet	Special warnings and precautions for use	Revision of text to read"Before initiating therapy with Augmentin careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity (see Contraindications). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to Augmentin(see Undesirable effects). If an allergic reaction occurs, Augmentin therapy should be discontinued, and appropriate alternative therapy instituted. Serious anaphylactic reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous (i.v.) steroids and airway management, (including intubation) may also be required. Augmentin should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin. Prolonged use may also occasionally result in overgrowth of non-susceptible organisms. Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately, and the patient investigated further. Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving Augmentin and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation. Changes in liver function tests have been observed in some patients receiving Augmentin. The clinical significance of these changes is uncertain. Augmentin should be used with caution in patients with evidence of hepatic dysfunction. Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for up to six weeks after treatment has ceased.	17/08/2022	GlaxoSmithKline Export Limited

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Augmentin 625mg, 1g tablet	Amoxicillin/ Clavulanic acid 625mg /1g tablet	Special warnings and precautions for use	In patients with renal impairment Augmentin dosage should be adjusted as recommended in the Dosage and Administration section. In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see Overdose)."	17/08/2022	GlaxoSmithKline Export Limited
			Interaction with other medicinal products and other forms of interaction	Revision of text to read"Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with Augmentin may result in increased and prolonged blood levels of amoxicillin. but not of clavulanic acid. Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of Augmentin and allopurinol. In common with other antibiotics, Augmentin may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. In the literature there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If coadministration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of Augmentin. In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure."		
			Pregnancy and lactation	Revision of text to read"Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered Augmentin have shown no teratogenic effects. In a single study in women with pre-term, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with Augmentin may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician. Augmentin may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for breast-fed infant."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Augmentin 625mg, 1g tablet	Amoxicillin/ Clavulanic acid 625mg /1g tablet	Undesirable effects	Insertion of text under subtitle Cardiac disorders to read"Very rare Kounis syndrome (see Special warnings and precautions for use)."	17/08/2022	GlaxoSmithKline Export Limited
4	Ciclosporin	Sandimmun Neoral	Warnings and Precautions	Addition of the heading "Driving and using machines " under this section. Addition of the text "Sandimmun Neoral may cause neurological and visual disturbances (see section ADVERSE DRUG REACTIONS). Caution should be exercised when driving a motor vehicle or operating machines. No studies on the effects of Sandimmun Neoral on the ability to drive and use machines have been performed." under the heading Driving and using machines	12/9/2022	Pfizer
				Revision of text under the heading Interactions increasing or decreasing ciclosporin levels to be considered to read "Various agents are known to either increase or decrease plasma or whole blood ciclosporin levels usually by inhibition or induction of enzymes involved in the metabolism of ciclosporin, in particular CYP3A4. Ciclosporin is a substrate of P-gp, hence inhibitors or inducers of P-gp may alter the concentrations of ciclosporin." Addition of the heading "Interactions resulting in decrease of other drug levels" under this section. Addition of the text "Concomitant administration of ciclosporin and mycophenolate sodium or mofetil in transplant patients may decrease the mean exposure of mycophenolic acid by 20-50% when compared with other immunosuppressants. This information should be taken into consideration when coadministering these drugs. The coadministration of a single dose of ciclosporin (200 mg or 600 mg) with a single dose of eltrombopag (50 mg) decreased plasma eltrombopag AUCinf by 18% to 24% and Cmax by 25% to 39%. This decrease in exposure is not considered clinically meaningful" under the heading Interactions resulting in decrease of other drug levels	2/9/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Ciclosporin	Sandimmun Neoral	Pregnancy, Lactation,females and males of Reproductive potential	Addition of the sub-heading "Risk summary" under the heading Pregnancy Addition of text "There are no adequate or well-controlled clinical studies in pregnant women using ciclosporin. There is a moderate amount of data on the use of Sandimmun Neoralciclosporin in pregnant patients from post-marketing experience, including published literature. Pregnant women receiving immunosuppressive therapies after transplantation, including ciclosporin and ciclosporin-containing regimens, are at risk of premature delivery (<37 weeks). The data have not demonstrated a higher incidence of miscarriages, major birth defects, or maternal events as compared to the rates seen in the general population (see HUMAN DATA). Embryo-fetal developmental (EFD) studies in rats and rabbits with ciclosporin have shown embryo-fetal toxicity at dose levels below the maximum recommended human dose (MRHD) based on body surface area (BSA) (see ANIMAL DATA). Sandimmun Neoral should not be used during pregnancy unless the expected benefit to the mother outweighs the potential risk to the fetus. The ethanol content should also be taken into account in pregnant women (see section WARNINGS AND PRECAUTIONS)." under the heading Risk summary Addition of the subheading "Human data" under heading Pregnancy Addition of the text"Published data from National Transplantation Pregnancy Registry (NTPR), described pregnancy outcomes in female kidney (482), liver (97), and heart (43) transplant recipients receiving ciclosporin. The data indicated successful pregnancies with a live birth rate of 76% and 76.9%, and 64% in kidney, liver, and heart transplant recipients, respectively. Premature delivery (<37 weeks) was reported in 52%, 35%, and 35% of kidney, liver, and heart transplant recipients, respectively.	2/9/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Ciclosporin	Sandimmun Neoral	Pregnancy, Lactation,females and males of Reproductive potential	The rates of miscarriages and major birth defects were reported to be comparable to the rates observed in the general population. No direct effect of ciclosporin on maternal hypertension, pre-eclampsia, infections, or diabetes can be established given the limitations inherent to registries and post-marketing safety reporting. A limited number of observations in children exposed to ciclosporin in utero is available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal." under the heading Human data Addition of the sub-heading "Animal data" under the heading Pregnancy Addition of the text "Three EFD studies (two oral and one intravenous) are available in rats. In oral EFD studies, pregnant rats were administered with ciclosporin either at doses of 10, 17, 30, 100 and 300 mg/kg/day or 4, 10 and 25 mg/kg/day from gestation day (GD) 6 to 15 or from GD 7 to 17, respectively. Maternal toxicity characterized by mortality, clinical signs of toxicity and impaired body weight gain were observed at 30 mg/kg/day and above. Ciclosporin was embryo- and fetotoxic as indicated by increased embryonic mortality and reduced fetal weight together with skeletal retardations in rats at 25 mg/kg/day and above. In addition, ventricular septal defect was observed at 25 mg/kg/day in fetuses. The no observed effect level (NOEL) for both dams and fetus was 17 mg/kg/day (below the MRHD based on BSA) after oral administration. In the other oral study, the NOEL for dams and fetuses were 10 and 4 mg/kg/day (below the MRHD based on BSA), respectively. In the IV EFD study, rats were administered with 3, 6 and 12 mg/kg/day of ciclosporin from GD 7 to 17. An increase in post implantation loss was observed at 12 mg/kg/day; ventricular septal defect was observed at 6 mg/kg/day and above in fetuses . The NOEL for dams and fetus were 6 and 3 mg/kg/day (below the MRHD based on BSA), respectively, after IV administration. In rabbits, ciclosporin was orally administered at dose levels of 10, 30, 100 or 300 mg/kg/day from GD 6 to 18. At 100 mg/kg/day and above, reduction in body weight gain of dams and at 300 mg/kg/day abortions were observed. Maternal toxicity, embryo-fetotoxicity as indicated by increased pre- and postnatal mortality, reduced fetal weight together with skeletal retardations were observed at 100 mg/kg/day and above. The NOEL for dams and fetuses was 30 mg/kg/day (below the MRHD based on BSA). In two published research studies, pregnant rabbits exposed to ciclosporin (10 mg/kg/day subcutaneously) during gestation demonstrated maternal toxicity (reduced body weight gain) and kidney changes in pups and adults (reduced numbers of nephrons, renal hypertrophy, systemic hypertension, and progressive renal insufficiency). An increase in fetal resorptions and a decrease in live pups and pup body weight were observed.	2/9/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Ciclosporin	Sandimmun Neoral	Pregnancy, Lactation,females and males of Reproductive potential	Revision of the heading to read as "Lactation" Addition of the subheading Risk summary under the heading Lactation Revision of the text under the subheading Risk summary to read "Ciclosporin is transferred into breast milk. Mothers receiving treatment with Sandimmun Neoral should not breast-feed. Because of the potential of Sandimmun Neoral to cause serious adverse drug reactions in breastfed newborns/infants, a decision should be made whether to abstain from breast-feeding or to abstain from using the medicinal drug, taking into account the benefit of breast-feeding for the newborn/infant and the importance of the medicinal product to the mother. The milk to maternal blood concentration ratio of ciclosporin was in the range of 0.17 to 1.4. Based on the infant milk intake, the highest estimated ciclosporin dose ingested by fully breast-fed infant was approximately 2% of maternal weight adjusted dose. The ethanol content of the Sandimmun Neoral formulations should also be taken into account (see section WARNINGS AND PRECAUTIONS)." Addition of the heading "Females and males of reproductive potential" under this section Addition of the sub-heading "Females" under the heading Females and males of reproductive potential. Addition of the text "There are no special recommendations for women of child-bearing potential." under the subheading Females Revision of the text under the heading Fertility to read"There is limited data on the effect of ciclosporin on human fertility. No impairment in fertility was demonstrated in male and female rats up to 5mg/kg/day (below MRHD based on BSA) (see Section NON-CLINICAL SAFETY DATA)."	2/9/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Ciclosporin	Sandimmun Neoral	Non-clinical safety data	Revision of text to under this section to read "Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, at doses of 1, 4, and 16 mg/kg/ day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-month rat study conducted at 0.5, 2, and 8 mg/kg/ day, pancreatic islet cell adenomas significantly exceeded the control rate at the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. Ciclosporin has not been found mutagenic/genotoxic in the Ames test, the v79–hgprt test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone marrow, the mouse dominant lethal assay, and the DNA repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by ciclosporin using human lymphocytes in vitro gave indication of a positive effect (i.e. induction of SCE) at high concentrations in this system. An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphoma and carcinomas of the skin. The risk of malignancies during ciclosporin treatment is higher than in the normal, healthy population, but similar to that in patients receiving other immunosuppressive therapies. It has been reported that reduction or discontinuance of immunosuppression may cause the lesions to regress. In a fertility study in rats, increased perinatal mortality and impaired postnatal development of F1 pups were observed at 15 mg/kg/day (below the MRHD based on BSA). No adverse effects on fertility and reproduction were observed up to 5 mg/kg/day (below the MRHD based on BSA) in male and female rats. For reproductive toxicity, see Section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL."	2/9/2022	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Enbrel	Etanercept	Fertility, pregnancy and lactation	Revision of text under the section to read "In lactating rats, following subcutaneous administration etanercept was excreted in the milk and detected in the serum of the pups. Etanercept has been reported to be excreted in human milk in insignificant amounts following subcutaneous administration and not detected in infant circulation Enbrel can be used during breastfeeding if clearly needed. While systemic exposure in a breastfed infant is expected to be low because etanercept is poorly excreted in the breast milk, the possibility to administer live vaccines to a breastfed infant when the mother is receiving etanercept should be carefully considered by the doctor.	12/9/2022	Pfizer
			Pharmacodynamic properties	Revision of text under the heading Pediatric population with juvenile idiopathic arthritis to read "Of the 127 patients in the parent study, 109 participated in the open-label extension study and were followed for an additional 8 years for a total of up to 10 years. At the end of the extension study, 84/109 (77%) patients had completed the study; 27 (25%) while actively taking Enbrel, 7 (6%) had withdrawn from treatment due to low/inactive disease; 5 (5%) had re-started Enbrel following an earlier withdrawal from treatment; and 45 (41%) had stopped Enbrel (but remained under observation); 25/109 (23%) patients permanently discontinued from the study."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	Imodium	Loperamide	What information must be known before taking Imodium 2 mg capsule	Revision of the text under the heading You should follow these dietary measures during treatment to read " o rehydrate yourself with abundant drinks, salted or sweetened, to compensate for the loss of liquid due to diarrhoea (the average daily water intake of an adult is 2 litres) o feed yourself sufficiently during the time of the diarrhoea, □ avoiding certain intakes and particularly milk, raw vegetables, fruits, green vegetables, spicy foods as well as chilled foods or beverages. □ favoring grilled meats, rice. • The use of this medicine is not recommended in patients with galactose intolerance, Lapp lactase deficiency or glucose or galactose malabsorption syndrome (rare hereditary diseases)."	2/9/2022	Janssen
			How to take Imodium 2 mg capsule	Revision of text under the heading Posology to read "Always take this medicine exactly as indicated by your doctor. If in doubt, consult your doctor or your pharmacist. • Acute diarrhea: The usual dosage is : In adult: start with 2 capsules, then after each unformed stool, take an additional capsule, without exceeding 8 capsules per day. In children over 8 years of age: start with 1 capsule, then after each unformed stool, take an additional capsule, without exceeding 6 capsules per day. • Chronic diarrhea: The usual dosage is: In adult: 1 to 3 capsules per day. In children over 8 years of age: 1 to 2 capsules per day."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	Imodium	Loperamide	What are the potential adverse effects	Revision of text under the heading Posology to read "Always take this medicine exactly as indicated by your doctor. If in doubt, consult your doctor or your pharmacist. • Acute diarrhea: The usual dosage is : In adult: start with 2 capsules, then after each unformed stool, take an additional capsule, without exceeding 8 capsules per day. In children over 8 years of age: start with 1 capsule, then after each unformed stool, take an additional capsule, without exceeding 6 capsules per day. • Chronic diarrhea: The usual dosage is: In adult: 1 to 3 capsules per day. In children over 8 years of age: 1 to 2 capsules per day."	2/9/2022	Janssen

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Nexium	Esomeprazole	Special warnings and precautions for use	Addition of text to read "This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'." under this section Addition of the text "Serious cutaneous adverse reactions (SCARs) such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening, have been reported very rarely in association with esomeprazole treatment. Patients should be advised of the signs and symptoms of the severe skin reaction EM/SJS/TEN/DRESS and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. Esomeprazole should be discontinued immediately upon signs and symptoms of severe skin reactions and additional medical care/close monitoring should be provided as needed. Re-challenge should not be undertaken in patients with EM/SJS/TEN/DRESS." under this section	26/09/2022	Astrazeneca
			Undesirable effects	Revision of text under the heading Skin and subcutaneous tissue disorders to read "Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS)"		
8	Pharmorubicin	Epirubicin hydrochloride	Preclinical safety data	Addition of text to read " The main target organs of toxicity following administration of epirubicin to animals were the hemolymphopoietic system, GI tract, heart, kidney, liver, and reproductive organs. Epirubicin was toxic to male and female reproductive organs in animal studies. In male rats, administration of epirubicin caused decreases in size/weight of the testes and/or epidiymides, and reduced spermatogenesis. In females, epirubicin caused gross alterations in the ovaries and uteri in rats and uterine atrophy in rats and dogs. Epirubicin was embryotoxic and teratogenic when administered during the period of organogenesis in pregnant rats, with an increased incidence of visceral abnormalities observed. However, no malformations were observed in rabbits	1/8/2022	Pfizer

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
8	Pharmorubicin	Epirubicin hydrochloride	Fertility, pregnancy and lactation	Addition of text to include "Based on animal studies, male and female fertility may be compromised (see Section 5.3). It is recommended to discuss fertility preservation with men and women prior to treatment	1/8/2022	Pfizer
9	Topamax	Topiramate	Special warnings and precautions for use	Revision of text under the heading Acute myopia and secondary angle closure glaucoma syndrome to read "A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include some or all of the following: myopia, mydriasis, anterior chamber shallowing, ocular hyperaemia (redness), choroidal detachments, retinal pigment epithelial detachments, macular striae, and increased intraocular pressure. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating topiramate therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in paediatric patients as well as adults. Treatment includes discontinuation of topiramate, as rapidly as possible in the judgment of the treating physician, and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure."	5/9/2022	Janssen
10	Zithromax	Azithromycin	Posology and method of administration	Revision of text under the sub-heading In Patients with Renal Impairment to read "No dose adjustment is necessary in patients with GFR 10–80 ml/min. Caution should be exercised when azithromycin is administered to patients with GFR <10 ml/min (see section 4.4 and section 5.2). Revision of text under the heading Renal impairment to read "In patients with GFR <10 ml/min, a 33% increase in systemic exposure to azithromycin was observed (see section 5.2)."	6/9/2022	Pfizer

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Zithromax	Azithromycin	Fertility, pregnancy and lactation	Revision of text under the heading Pregnancy to read "Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the fetus due to azithromycin was found. There is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period. While most studies do not suggest an association with adverse fetal effects such as major congenital malformations or cardiovascular malformations, there is limited epidemiological evidence of an increased risk of miscarriage following azithromycin exposure in early pregnancy. Azithromycin should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any small increased risks which may exist."	6/9/2022	Pfizer
			Pharmacokinetic properties	Revision of text under the sub- heading Renal Impairment to read "The pharmacokinetics of azithromycin in subjects with GFR 10-80 ml/min were not affected following a single 1 gram dose of immediate-release azithromycin. Statistically significant differences in AUC0-120 (8.8 µg·h/ml vs. 11.7 µg·h/ml), Cmax (1.0 µg/ml vs. 1.6 µg/ml) and CLr (2.3 ml/min/kg vs. 0.2 ml/min/kg) were observed between the group with GFR <10 ml/min and GFR >80 ml/min.		
11	Zometa	Zoledronic acid(4 mg/100 mL solution for infusion)	Pregnancy, Lactaton, Females and males of reproductive potential	Revision of text under subtitle Infertility to read"The fertility was decreased in rats dosed subcutaneously with 0.01 mg/kg/day of zoledronic acid. There are no data available in humans."	1/8/2022	Novartis