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	Aprovasc	Amlodipine/ Irbesartan	Pharmacokinetics and Pharmacodynamics	Revision of text to read "Patients with hepatic failure: see General Precautions." under this section.	12-May-20	Sanofi
			Contraindication	Deletion of text "Hypotension: volume-depleted patients: Irbesartan has been rarely associated with hypotension in hypertensive patients without other co-morbid conditions. As with ACE inhibitors, symptomatic hypotension may be expected to occur in sodium/volume-depleted patients and in those undergoing intensive diuretic treatment and/or salt restriction, or on hemodialysis. Volume and/or and sodium depletion should be corrected before therapy with APROVASC® is initiated or the lowest possible starting dose should be considered. Fetal/neonatal morbidity and mortality: Although there is no experience with irbesartan in pregnant women, in utero exposure to ACE inhibitors given to pregnant women during the second and third trimesters of gestation has been reported to cause injury to and death of the developing fetus. Thus, as for any drug that acts directly on the renin-angiotensin-aldosterone system, APROVASC® should not be used during pregnancy. If pregnancy is detected during treatment, APROVASC® should be discontinued as soon as possible. Patients with heart failure: In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischemic etiology, amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening of heart failure compared to placebo (see Pharmacodynamics). Hepatic impairment: As with other calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and no dosage recommendations have been established in this population. APROVASC® should therefore be administered with caution in these patients. Hypertensive crisis: The safety and efficacy of APROVASC® in the treatment of hypertensive crisis have not been established." under the heading Warnings.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	Aprovasc	Amlodipine/ Irbesartan	General precautions	Addition of text to read "The use of APROVASC® in patients with psoriasis or with a history of psoriasis should be weighed carefully as it may exacerbate psoriasis." under this section. Revision of text to read "Pediatric use: Safety and efficacy in pediatric patients have not been established. Geriatric use: In elderly patients, with volume depletion (including those on therapy with diuretics), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, can cause a deterioration of renal function, including a possible acute renal failure. These effects are usually reversible. Renal function should be monitored periodically in patients receiving periodic treatment with Irbesartan and NSAIDs. The antihypertensive effect of angiotensin II receptor antagonists can be attenuated by NSAIDs including selective COX-2 inhibitors. In patients receiving Irbesartan in clinical studies no overall differences were observed in terms of efficacy and safety in older patients (65 years or older) or in younger patients. Hypotension: patients with volume depletion: Irbesartan has rarely been associated with hypotension in hypertensive patients who have no other concomitant condition. Symptomatic hypotension may occur, such as with ACE inhibitors, in patients with sodium/volume depletion and in those under intensive treatment with diuretics and/or salt restriction or in hemodialysis. The depletion of volume and/or sodium should be corrected before starting treatment with APROVASC® or the start of treatment with the lowest possible dose should be considered. Patients with heart failure: In a long-term placebo-controlled study (PRAISE-2) of amlodipine in patients with non-ischemic etiology heart failure class NYHA III and IV, the use of amlodipine was associated with an increase in the reports of pulmonary edema although there was no significant difference in the incidence of heart failure worsening when compared with placebo (see Pharmacodynamics). Hepatic impairment: As with other calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and no dose recommendations have been established for them. Therefore, APROVASC® should be administered with caution in these patients. Hypertensive crisis: The safety and efficacy of APROVASC® in the treatment of hypertensive crisis has not been established. Lithium: The concomitant use of angiotensin II receptor blockers and calcium channel blockers may reduce renal lithium clearance and the increase of serum levels that may reach toxic levels. Lithium levels should be monitored in patients who are receiving APROVASC." under this section.	12-May-20	Sanofi
			Restrictions on use during pregnancy and lactaion	Addition of text to read "Although there is no experience with Irbesartan in pregnant women, it has been reported that exposure of the pregnancy product to ACE inhibitors, administered to pregnant women during the second and third quarters of pregnancy, causes injuries and death of the fetus. Therefore, as any other drug acting directly on the renin-angiotensin-aldosterone system, APROVASC® should not be administered during pregnancy. When pregnancy is detected during treatment, APROVASC® should be discontinued as soon as possible." under Fetal/neonatal morbidity and mortality.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	Aprovasc	Amlodipine/ Irbesartan	Secondary and Adverse reactions	Addition of "Blood and lymphatic system disorders" as a System Organ Class and "Thrombocytopenia (including thrombocytopenic purpura)" as a reaction with frequency Not Known. Addition of Not Known as a frequency in "Table 3: Adverse events reported in clinical trials with Irbesartan or in post-marketing reports" under this section. Revision of text to read "Hypersensitivity reactions (anaphylactic reactions including anaphylactic shock)" with frequency Not known under Immune system disorders. Revision of text to read "Angioedema, urticaria, photosensitivity, psoriasis (and psoriasis exacerbation)" with frequency Not known under Skin and subcutaneous tissue disorders.	12-May-20	Sanofi
			Drug-drug and other interractions	Addition of text to read "Based on the experience with the use of other medications that affect the renin-angiotensin system, the concomitant use of Irbesartan with potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other medications that may increase kalaemia with irbesartan can cause an increase in serum potassium, sometimes severe, and requires close monitoring of serum potassium." under Irbesartan. Revision of text to read "Amlodipine has been safely administered concomitantly with thiazide diuretics, beta blockers, alpha blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs." under Amlodipine.		
2	Bicalutamide	Bicalutamide	Contraindications	Modification of text to read "Hypersensitivity to the active substance or to any of the excipients" under this section.	23-Mar-20	Sandoz
			Special warnings and precautions for use	Addition of text to read "Potentiation of the effects of coumarin anticoagulants in patients concomitantly receiving bicalutamide may result in an increase in prothrombin time (PT) and International Normalised Ratio (INR). Some of these cases have been associated with a bleeding risk. Close monitoring of PT/INR is therefore recommended and adjustment of the anticoagulant dose should be considered. Antiandrogen therapy may cause morphological changes in spermatozoa. Although the effect of bicalutamide on sperm morphology has not been evaluated and no such changes have been reported for patients who received bicalutamide, patients and/or their partners should follow adequate contraception during and for 130 days after bicalutamide therapy" under this section.		
			Interaction with other medicinal products and other forms of interaction	Modification of text to read "There have been reports of an increased effect of warfarin and other coumarin anticoagulants when administered concomitantly with bicalutamide. It is therefore recommended that in patients who are receiving coumarin anticoagulants, prothrombin time should be closely monitored. A dose adjustment of the anticoagulant medicinal product should be considered". under this section.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Bicalutamide	Bicalutamide	Pregnancy and lactation	Addition of text under breast feeding to read "Bicalutamide is contraindicated during breast-feeding". Addition of text under fertility to read "Reversible impairment of male fertility has been observed in animal studies (see section 5.3). A period of sub-fertility or infertility should be assumed in man" .	23-Mar-20	Sandoz
			Undesirable effects	Addition of text to read "Increase of PT/INR During post-marketing cases of interactions between coumarin anticoagulants and bicalutamide have been reported" under this section.		
			Pharmacodynamic properties	Addition of new information under clinical efficacy and safety text .		
			Pharmacokinetic properties	Addition of text to read "Steady state plasma concentration of the (R)-enantiomer of aprroximately 22 µg/ml are observed during daily asministration of 150 mg doses of bicalutamide". under this section.		
				Modification of text under biotransformation and elimination to read "In a clinical study the mean concentration of (R)-bicalutamide in semen of men receiving bicalutamide 150 mg was 4.9 µg/ml. The amount of bicalutamide potentially delivered to a female partner during intercourse is low and equates to approximately 0.3 µg/kg. This is below that required to induce changes in offspring of laboratory animals" .		
			Preclinical Safety Data	Addition of text to read "Bicalutamide is a potent antiandrogen and a mixed function oxidase enzyme inducer in animals. [Bicalutamide - 50 mg film-coated tablet only] -Target organ changes, including tumour induction, in animals, are related to these activities. None of the findings in the preclinical testing is considered to have relevance to the treatment of advanced prostate cancer patients. [Bicalutamide - 150 mg film-coated tablet only] - Target organ changes, including tumour induction (Leydig cells, thyroid, liver) in animals, are related to these activities. Enzyme induction has not been observed in man and none of these findings is considered to have relevance to the treatment of patients with prostate cancer. Atrophy of seminiferous tubules is a predicted class effect with antiandrogens and has been observed for all species examined. Full reversal of testicular atrophy was 24 weeks after a 12 month repeated dose toxicity study in rats, although functional reversal was evident in reproduction studies 7 weeks after the end of an 11 week dosing period. A period of subfertility or infertility should be assumed in man." under this section.		
			List of excipients	Addition of text to read "Tablet core: Lactose monohydrate, Sodium starch glycolate type A, Povidine K30 (E1201), Maize starch, Magnesium stearate (E572). Tablet coating: [Bicalutamide - 50 mg film-coated tablet only]- Methylcellulose, Titanium dioxide (E171), Triacetin (E1518). [Bicalutamide - 150 mg film-coated tablet only] -Hypromellose, Titanium dioxide (E171), Macrogol Polysorbate 80" under this section.		
			Shelf Life	Change of shelf life to read " 2 years" under this section.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Bicalutamide	Bicalutamide	Special precautions for storage	Addition of text to read "This medicinal product does not require any special storage conditions". Under this section.	23-Mar-20	Sandoz
3	Celecoxib	Celecoxib	Special warnings and precautions for use	Revision of text to read "Upper and lower gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with celecoxib. Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or platelet aggregation inhibitors (acetylsalicylic acid), or glucocorticoids concomitantly, patients using alcohol, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding." under Gastrointestinal (GI) effects.	12-May-20	Sandoz
			Posology and method of administration	Additionof text to read " For patients who have difficulty swallowing capsules, the contents of a celecoxib capsule can be added to applesauce, rice gruel, yogurt or mashed banana. To do so, the entire capsule contents must be carefully emptied onto a level teaspoon of cool or room temperature applesauce, rice gruel, yogurt or mashed banana and should be ingested immediately with 240 ml of water. The sprinkled capsule contents on applesauce, rice gruel or yogurt are stable for up to 6 hours under refrigerated conditions (2-8°C). The sprinkled capsule contents on mashed banana should not be stored under refrigerated conditions and should be ingested immediately." under Method of administration.		
4	Diprofos	Betamethasone dipropionate	Special warnings and precautions for use	Addition of text to read "Rare instances of anaphylactoid/anaphylactic reactions with a possibility of shock have occurred in patients receiving parenteral corticosteroid therapy. Appropriate precautionary measures should be taken with patients who have a history of allergic reactions to corticosteroids. " under Antiseptic techniques are necessary. Addition of text to read "Visual disturbance may be reported with systemic and topical (including, intranasal, inhaled and intraocular) corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes of visual disturbances which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids." under Visual disturbance.	20-May-20	MSD
			Undesirable effects	Addition of "Vision blurred (see also section 4.4). " to reactions under Ophthalmic disorders.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Doxorubicin	Doxorubicin	Special warnings and precautions for use	disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones and concomitant use of drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g., trastuzumab). Anthracyclines including doxorubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored (see section 4.5). Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The reported half-life of trastuzumab is approximately 28-38 days and may persist in the circulation for up to 27 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended. " under this section. Addition of heading "Tumour-Lysis Syndrome" under this section. Addition of " Vaccinations-Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including doxorubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving doxorubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished (see section 4.5)." under the heading Additional warning and precautions for other routes of administration.	12-May-20	Sandoz
			Interaction with other medicinal products and other forms of interaction	Addition of text to read " Literature reports suggest that adding cyclosporine to doxorubicin results in more profound and prolonged haematologic toxicity than that observed with doxorubicin alone. Coma and seizures have also been described with concomitant administration of cyclosporine and doxorubicin (see section 4.4). " under this section.		
6	Esmeron	Rocuronium bromide	Undesirable effects	Addition of "Kounis syndrome " with a frequency "Not known" under this section. Revision of text to read "Post-marketing surveillance data cannot give precise incidence figures. For that reason, the reporting frequency was divided over three rather than five categories. " under the heading Tabulated list of adverse reactions. Addition of headings "Summary of the safety profile and Tabulated list of adverse reactions " under the section.	20-May-20	MSD
7	Ivanz	Ertapenem.	Pharmacodynamic properties	Addition of " Acute Generalised Exanthema sis (AGEP)" as an adverse reaction under Skin and subcutaneous tissue disorders with frequency Not known.	13-May-20	MSD

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Ivanz	Ertapenem.	Pharmacodynamic properties	Revision of text to read" The EUCAST MIC breakpoints are as follows: • Enterobacterales: S ≤ 0.5 mg/L and R > 0.5 mg/L • Streptococcus pneumoniae: S ≤ 0.5 mg/L and R > 0.5 mg/L • Haemophilus influenzae: S ≤ 0.5 mg/L and R > 0.5 mg/L • M. catarrhalis: S ≤ 0.5 mg/L and R > 0.5 mg/L • Gram negative anaerobes: S ≤ 0.5 mg/L and R > 0.5 mg/L • Gram positive anaerobes: S ≤ 0.5 mg/L and R > 0.5 mg/L • Viridans group streptococci: S ≤ 0.5 mg/L and R > 0.5 mg/L • Non species related breakpoints: S ≤ 0.5 mg/L and R > 0.5 mg/L (NB: Susceptibility of staphylococci to ertapenem is inferred from methicillin susceptibility and susceptibility of group A, B, C, & G streptococci is inferred from benzylpenicillin susceptibility) " under Breakpoints.	13-May-20	MSD
8	Metformin	Metformin	Posology and method of administration	Addition of text under posology to read "Adults with normal renal function (GFR ≥90 ml/min)" .	23-Mar-20	Sandoz
				Modification of text under special populations to read "A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months". Addition of table under renal impairment.		
				Modification of text to read "Elderly :As metformin is excreted via the kidneys, and elderly patients tend to exhibit decreased renal function, elderly patients taking metformin should have their renal function monitored regularly. Metformin dose should be adjusted based on renal function" under this section.		
			Contraindications	Modification of text under renal impairment to read "Severe renal failure (GFR <30 ml/min)". Modification of text under metabolic acidosis to read "Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)".		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
8	Metformin	Metformin	Special warnings and precautions for use	Additon of text under lactic acidosis to read " Lactic acidosis, a very rare but serious metabolic complication,most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended. Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (<7.35), increased plasma lactate levels (>5 mmol/l) and an increased anion gap and lactate/pyruvate ratio.". Modification of text under renal function read "GFR should be assessed before treatment initiation and regularly thereafter (see section 4.2). Metformin is contraindicated in patients with GFR<30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function" .	23-Mar-20	Sandoz
				Modification of text under Administration of iodinated contrast agents to read "Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable" . Modification of text under surgery to read "Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable".		
			Interaction with other medicinal products and other forms of interaction	Modification of text under Concomitant use not recommended to read "Alcohol Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment". Addition of text under Iodinated contrast agents to read "Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable".		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
8	Metformin	Metformin	Interaction with other medicinal products and other forms of interaction	adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary". Addition of text under others to read "Certain medicinal products tend to cause hyperglycaemia and may lead to loss of glycaemic control. These medicinal products include the thiazides and other diuretics, corticosteroids,	23-Mar-20	Sandoz
			Undesirable effects	Modification of text to read " A decrease in vitamin B12 absorption with decreased serum levels has very rarely been observed in patients treated long-term with metformin and appears to generally not be of clinical significance. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia"		
			Overdose	Modification of text to read "Overdose of metformin has occurred, including ingestion of amounts greater than 50 g. Hypoglycaemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialysable with a clearance of up to 170 ml/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated active substance from patients in whom metformin overdose is suspected. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms".		
			Pharmacodynamic properties	Modification of text to read " Pharmacotherapeutic group: Drugs used in diabetics; blood glucose lowering drugs, excl. insulins; biguanides".Modification of text under pharmcodynamics to read "In humans, metformin hydrochloride has favourable effects on lipid metabolism, independently of its action on glycaemia. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDLc and triglyceride levels.".		
			Special populations	Modification of text under Hepatic impairment to read "No pharmacokinetic studies of metformin hydrochloride have been conducted in subjects with hepatic impairment".		
9	Ramipril	Ramipril	Contraindications	Additionof text to read "Concomitant use with sacubitril/valsartan therapy; Ramipril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.4 and 4.5). " under this section.	12-May-20	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
9	Ramipril	Ramipril	Special warnings and precautions for use	Modification of text to read "This risk of angioedema may be increased in patients taking concomitant medications which may cause angioedema such as mTOR (mammalian target of rapamycin) inhibitors (e.g. temsirolimus, everolimus, sirolimus); vildagliptin or neprilysin (NEP) inhibitors (such as racecadotril). " under this section. Addition of "Hypersensitivity / angioedema-Concomitant use of ramipril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of ramipril. Treatment with ramipril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5). Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor." under this section. Modification of text to read "Electrolyte monitoring Serum Potassium ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5)."	12-May-20	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
9	Ramipril	Ramipril	Interaction with other medicinal products and other forms of interaction	Addition of text to read "Medicines increasing the risk of angioedema- Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4). Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4) " under Contraindicated combinations. Addition of text to read"Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes- Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with ramipril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassiumcontaining salt substitutes may lead to significant increases in serum potassium. Care should also be taken when ramipril is coadministered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of ramipril with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium." under Contraindicated combinations. Modification of text to read "Ciclosporin-Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended." under Contraindicated combinations. Modification of text to read "Heparin-Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended." under Contraindicated combinations. Modification of text to read "Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent." under Contraindicated combinations. Modification of text to read "Neprilysin (NEP) inhibitors-An increased risk of angioedema has been reported with concomitant use of ACE inhibitors and NEP inhibitor such as racecadotril (see section 4.4)." under Precautions for use .	12-May-20	Sandoz
10	Triveram	Atorvastatin /Perindopril arginine/Amlodipine	Contraindications	Addition of text to read "• Concomitant use with sacubitril/valsartan (see sections 4.4 and 4.5), • Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5), • Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney (see section 4.4)." under this section.	11-May-20	Les Laboratoires Servier

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Triveram	Atorvastatin /Perindopril arginine/Amlodipine	Special warnings and precautions for use	Revision of text to read "In such situations, the risk of treatment should be regularly considered in relation to possible benefit, and regular clinical monitoring is recommended. If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started." Revision of text to read "Whilst on treatment: • Patients must be asked to promptly report any unexplained muscle pain, cramps, or weakness especially if accompanied by malaise or fever." Addition of text to read "Due to atorvastatin component, TRIVERAM must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of TRIVERAM and fusidic acid should only be considered on a case by case basis and under close medical supervision." under the heading Concomitant treatment with other medicinal products. Deletion of text " The concomitant use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin may be considered during fusidic acid therapy (see section 4.5)" under the heading Concomitant treatment with other medicinal products." Addition of " Renovascular hypertension- There is an increased risk of hypotension and renal insufficiency when patient with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors (see section 4.3). Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis. " under this section.	11-May-20	Les Laboratoires Servier

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Triveram	Atorvastatin /Perindopril arginine/Amlodipine	Special warnings and precautions for use	Revision of text to read "Renal impairment- TRIVERAM can be administered in patients with creatinine clearance ≥ 60mL/min, and is not suitable for patients with creatinine clearance < 60mL/min (moderate to severe renal impairment). In these patients, an individual dose titration with the monocomponents is recommended. Routine monitoring of potassium and creatinine are part of normal medical practice for patients with renal impairment (see section 4.8). In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors,may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or TRIVERAM may be required. Amlodipine may be used at normal doses in patients with renal failure. Changes in amlodipine plasma concentration are not correlated with degree of renal impairment. Amlodipine is not dialysable The effect of the combination TRIVERAM has not been tested in patients with renal impairment. TRIVERAM doses should respect the dosing recommendations of the individual components taken separately." under this section. Addition of text to read "The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of perindopril therapy. If treatment with sacubitril/valsartan is stopped, perindopril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5). Concomitant use of other NEP inhibitors (e.g. racecadotril) and ACE inhibitors may also increase the risk of angioedema (see section 4.5) Hence, a careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors (e.g. racecadotril) in patients on perindopril. Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus): Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). " under Hypersensitivity/Angioedema.	11-May-20	Les Laboratoires Servier

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Triveram	Atorvastatin /Perindopril arginine/Amlodipine	Special warnings and precautions for use	Revision of text to read "Hyperkalaemia-Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium- containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above- mentioned agents with TRIVERAM is deemed necessary, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5)." under this section. Revision of text to read "Combination with lithium- The combination of lithium and medicines containing perindopril, is generally not recommended (see section 4.5)." under this section. Addition of text to read"Primary aldosteronism- Patients with primary hyperaldosteronism generally will not respond to anti-hypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of this product is not recommended for those patients." under this section. Revision of text to read"Excipients- Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose- galactose malabsorption, or the total lactase deficiency should not take TRIVERAM." under this section. Addition of text to read"Level of sodium- TRIVERAM contains less than 1 mmol sodium (23 mg) per tablet, i.e. is essentially ‘sodium-free’." under this section.	11-May-20	Les Laboratoires Servier

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10			Interaction with other medicinal products and other forms of interaction	Addition of text to read" Extracorporeal treatments -Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent." under known interactions with Perindopril in a concomitant use contraindicated table under this section. Addition of text to read" Sacubitril/valsartan-The combination of perindopril with sacubitril/valsartan is contraindicated, because concomitant inhibition of neprilysine and ACE may increase the risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of perindopril therapy. Perindopril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4)."under known interactions with Perindopril in a concomitant use contraindicated table under this section. Revision of text to read "CYP450 3A4 inhibitors- Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1. Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe (see section 4.4). Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see table 1 and the specific information below). Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) with TRIVERAM should be avoided if possible. In cases where co-administration of these medicinal products with TRIVERAM cannot be avoided, a lower initial doses and a lower maximum dose of atorvastatin in TRIVERAM should be considered and appropriate clinical monitoring of the patient is recommended (see table 1)."under known interactions with Atorvastatin in a concomitant use not recommended table under this section.	11-May-20	Les Laboratoires Servier

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Triveram	Atorvastatin /Perindopril arginine/Amlodipine	Interaction with other medicinal products and other forms of interaction	Addition of text to read "Co-trimoxazole (trimethoprim/sulfamethoxazole) Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4)." under known interactions with Perindopril in a concomitant use not recommended table under this section. Addition of text to read "Potassium-sparing diuretics (e.g. triamterene, amiloride, eplerenone, spironolactone), potassium (salts) Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects). The combination of TRIVERAM with these drugs is not recommended (see section 4.4). If concomitant use is nonetheless indicated, they should be used with caution and with frequent monitoring of serum potassium. These drugs are known to induce hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects). The combination of Triveram with these drugs is not recommended (see section 4.4). If concomitant use is nonetheless indicated, they should be used with caution and with frequent monitoring of serum potassium."under known interactions with Perindopril in a concomitant use not recommended table under this section.	11-May-20	Les Laboratoires Servier

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Triveram	Atorvastatin /Perindopril arginine/Amlodipine	Interaction with other medicinal products and other forms of interaction	Addition of text to read" Fusidic acid-The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with systemic fusidic acid is necessary, TRIVERAM treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4)." under known interactions with Atorvastatin in a concomitant use not recommended table under Concomitant use which requires special care. Revision of text to read"Antidiabetic agents (insulins, oral hypoglycaemic agents) Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment." under known interactions with Perindopril in a concomitant use not recommended table under Concomitant use which requires special care. Addition of text to read "Racecadotril- ACE inhibitors (e.g. perindopril) are known to cause angioedema. This risk may be elevated when used concomitantly with racecadotril (a drug used against acute diarrhea)." under known interactions with Perindopril in a concomitant use not recommended table under Concomitant use which requires special care. Addition of text to read "mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) -Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.4)." under known interactions with Perindopril in a concomitant use not recommended table under Concomitant use which requires special care.	11-May-20	Les Laboratoires Servier

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Triveram	Atorvastatin /Perindopril arginine/Amlodipine	Interaction with other medicinal products and other forms of interaction	Addition of text to read "There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co administered with clarithromycin." under CYP3A4 inhibitors under known interactions with Amlodipine in a concomitant use which requires special care table. Addition of text to read"Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum). under CYP3A4 inhibitors CYP3A4 inducers under known interactions with Amlodipine in a concomitant use which requires special care table. Revision of text to read "Digoxin, atorvastatin or warfarin- In clinical interactions studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin ." under known interactions with Amlodipine in a concomitant use to be taken into consideration table. Addition of text to read "Tacrolimus-There is a risk of increased tacrolimus blood levels when co administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate. Mechanistic Target of Rapamycin (mTOR) Inhibitors - mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors. Ciclosporine-No drug interaction studies have been conducted with ciclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of ciclosporine were observed. Consideration should be given for monitoring ciclosporine levels in renal transplant patients on amlodipine, and ciclosporine dose reductions should be made as necessary. **under known interactions with Amlodipine in a concomitant use to be taken into consideration table.**	11-May-20	Les Laboratoires Servier
				Addition of dosage "Colestipol 10 g BID, 24 weeks 40 mg OD for 8 weeks 0.74** No specific recommendation." under a table Effect of co-administered medicinal product on the pharmacokinetics of atorvastatin.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Triveram	Atorvastatin /Perindopril arginine/Amlodipine	Fertility, pregnancy and lactation	Addition of text to sub-heading Perindopril to read "Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy." under Pregnancy. Deletion of text "Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. " from sub-heading Perindopril under Pregnancy. Addition of text to sub-heading Amlodipine to read **"Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown." under Breast-feeding.** **Deletion of text "It is not known whether amlodipine is excreted in breast milk" from the sub-heading Amlodipine under Breast-feeding.**	11-May-20	Les Laboratoires Servier
			Effects on ability to drive and use machines	Revision of text to read "• Perindopril has no direct influence on the ability to drive and use machines but dizziness or fatigue related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication. " under this section.		
			Undesirable effects	Revision of text to read "The most commonly reported adverse reactions with atorvastatin, perindopril and amlodipine given separately include: nasopharyngitis, hypersensitivity, hyperglycaemia, headache, pharyngolaryngeal pain, epistaxis, constipation, flatulence, dyspepsia, nausea, diarrhoea, change of bowel habit, myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, ankle swelling, back pain, liver function test abnormal, blood creatine kinase increased, somnolence, dizziness, palpitations, flushing, dyspnoea, abdominal pain, oedema, fatigue, paraesthesia, visual impairment, diplopia, tinnitus, vertigo, hypotension, cough, dyspnoea, vomiting, dysgeusia, rash, pruritus, asthenia." under Summary of the safety profile.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Triveram	Atorvastatin /Perindopril arginine/Amlodipine	Undesirable effects	Reclassification of adverse events as follows: Stroke possible secondary to excessive hypotension in high-risk patients (see section 4.4) as very rare under Nervous system for Perindopril. Extrapyramidal disorder (extrapyramidal syndrome) as Not known under Nervous system for Amlodipine. Visual impairment as Common under Eye disorders for Amlodipine. Diplopia as Common under Eye disorders for Amlodipine. Vertigo as Common under Ear and Labyrinth disirders for Perindopril. Myocardial infarction, possibly secondary to excessive hypotension in high- risk patients (see section 4.4) as Very rare under Cardiac disorders for Perindopril and Amlodipine. Raynaud's phenomenon as Not Known for Perindopril. Cough as Uncommon under Respiratory, thoracic and mediastinal disorders for Amlodipine. Dyspnoea as Common under Respiratory, thoracic and mediastinal disorders for Amlodipine. Dyspepsia as Common under Gastrointestinal disorders for Amlodipine. Change of bowel habit as Common under Gastrointestinal disorders for Amlodipine. Urticaria as Uncommon under Skin and subcutaneous tissue disorders for Amlodipine. Psoriasis aggravation as Rare under Skin and subcutaneous tissue disorders for Perindopril. Toxic epidermal necrolysis as Not known under Skin and subcutaneous tissue disorders for Amlodipine. Asthenia as Common under General disorders and administration site conditions for Amlodipine. Oedema as Very common under General disorders and administration site conditions for Amlodipine. Haemoglobin decreased and haematocrit decreased as Very rare under Investigations for Perindopril. Deletion of text "Exceptional cases of extrapyramidal syndrome have been reported with amlodipine." under Summary of the safety profile. Addition of text to read "Cases of SIADH have been reported with other ACE inhibitors. SIADH can be considered as a very rare but possible complication associated with ACE inhibitor therapy including perindopril." under Summary of the safety profile.	11-May-20	Les Laboratoires Servier

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
10	Triveram	Atorvastatin /Perindopril arginine/Amlodipine	Pharmacodynamic properties	Revision of text under Prevention of cardiovascular disease for Atorvastatin to read "Pharmacotherapeutic group: Lipid modifying agents, HMG CoA reductase inhibitors, other combinations, ATC code: C10BX11" under this section. Revision of text to read"ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) is an international randomised trial with a 2x2 factorial design. ASCOT aimed to compare the effects of two antihypertensive treatment regimens in 19,257 patients (Blood Pressure Lowering Arm – ASCOT-BPLA) and the effects of the addition of atorvastatin 10 mg, compared with placebo, in addition to an antihypertensive treatment in 10,305 patients (Lipid Lowering Arm – ASCOT-LLA) on non-fatal and fatal coronary events." under Clinical efficacy and safety. Revision of text under Prevention of cardiovascular disease for Atorvastatin to read"In a subgroup of patients from ASCOT-LLA defined in a post-hoc analysis concurrently treated with atorvastatin, perindopril and amlodipine (n=1,814), there was a 38% reduction of fatal coronary events and non-fatal myocardial infarction (95%CI [0.36; 1.08]) in comparison with atorvastatin, atenolol and bendroflumethiazide (n=1,978). There were also a significant reduction of 24% for total cardiovascular events and revascularization procedures (95%CI [0.59;0.97]), a reduction of 31% for total coronary events (95%CI [0.48;1.00]) and a significant reduction of 50% for fatal and non fatal stroke (95%CI [0.29;0.86]), 39% for the composite of non-fatal myocardial infarction, fatal coronary events and coronary revascularization procedures (95%CI (0.38;0.97]) and 42% for the composite of cardiovascular mortality, myocardial infarction and stroke (95%CI [0.40;0.85])." under Clinical efficacy and safety.	11-May-20	Les Laboratoires Servier
			Pharmacokinetic properties	Revision of text to read"Linearity/ non linearity-It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure." under Perindopril.		
11	Vancomycin	Vancomycin	Therapeutic indications	Addition of text to read "Vancomycin is indicated in all age groups for the treatment of the following infections (see sections 4.2, 4.4 and 5.1) - complicated skin and soft tissue infections (cSSTI) - bone and joint infections - community acquired pneumonia (CAP) - hospital acquired pneumonia (HAP), including ventilatorassociated pneumonia (VAP) - infective endocarditis Vancomycin is also indicated in all age groups for the perioperative antibacterial prophylaxis in patients that are at high risk of developing bacterial endocarditis when undergoing major surgical procedures" under this section	12-May-20	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Vancomycin	Vancomycin	Posology and administration.	Addition of "Posology Where appropriate, vancomycin should be administered in combination with other antibacterial agents. " under this section. Modification of text to read "Intravenous administration The initial dose should be based on total body weight. Subsequent dose adjustments should be based on serum concentrations to achieve targeted therapeutic concentrations. Renal function must be taken into consideration for subsequent doses and interval of administration. Patients aged 12 years and older -The recommended dose is 15 to 20 mg/kg of body weight every 8 to 12 h (not to exceed 2 g per dose). " under this section. Addition of text to read "In seriously ill patients, a loading dose of 25–30 mg/kg of body weight can be used to facilitate rapid attainment of target trough serum vancomycin concentration. " under this section. Modification of text to read "Infants and children aged from one month to less than 12 years of age The recommended dose is 10 to 15 mg/kg body weight every 6 hours (see section 4.4). Term neonates (from birth to 27 days of post-natal age) and preterm neonates (from birth to the expected date of delivery plus 27 days) For establishing the dosing regimen for neonates, the advice of a physician experienced in the management of neonates should be sought. One possible way of dosing vancomycin in neonates is illustrated in the following table: (see section 4.4) , with the addition of a dosing interval table." under this section. Modification of text to read" Peri-operative prophylaxis of bacterial endocarditis in all age groups The recommended dose is an initial dose of 15 mg/kg prior to induction of anaesthesia. Depending on the duration of surgery, a second vancomycin dose may be required. Duration of treatment Suggested treatment duration is shown in table below. In any case, the duration of treatment should be tailored to the type and severity of infection and the individual clinical response. and the addition of a treatment duration per indication table." under this section. Modification of text to read " Renal impairment In adult and paediatric patients with renal impairment, consideration should be given to an initial starting dose followed by serum vancomycin trough levels rather than to a scheduled dosing regimen, particularly in patients with severe renal impairment or those who undergo renal replacement therapy (RRT) due to the many varying factors that may affect vancomycin levels in them. In patients with mild or moderate renal failure, the starting dose must not be reduced. In patients with severe renal failure, it is preferable to prolong the interval of administration rather than administer lower daily doses. Appropriate consideration should be given to the concomitant administration of medicinal products that may reduce vancomycin clearance and/or potentiate its undesirable effects (see section 4.4). "	12-May-20	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Vancomycin	Vancomycin	Posology and administration	Modification of text to read "Vancomycin is poorly dialysable by intermittent haemodialysis. However, use of high-flux membranes and continuous renal replacement therapy (CRRT) increases vancomycin clearance and generally requires replacement dosing (usually after the haemodialysis session in case of intermittent haemodialysis). Adults Dose adjustments in adult patients could be based on glomerular filtration rate estimated (eGFR) by the following formula Men: [Weight (kg) x 140 - age (years)]/ 72 x serum creatinine (mg/dl) Women: 0.85 x value calculated by the above formula. The usual starting dose for adult patients is 15 to 20 mg/kg that could be administered every 24 hours in patients with creatinine clearance between 20 to 49 ml/min. In patients with severe renal impairment (creatinine clearance below 20 ml/min) or those on renal replacement therapy, the appropriate timing and amount of subsequent doses largely depend on the modality of RRT and should be based on serum vancomycin trough levels and on residual renal function (see section 4.4). Depending on the clinical situation, consideration could be given to withhold the next dose while awaiting the results of vancomycin levels. In the critically ill patient with renal insufficiency, the initial loading dose (25 to 30 mg/kg) should not be reduced. Paediatric population Dose adjustments in paediatric patients aged 1 year and older could be based on glomerular filtration rate estimated (eGFR) by the revised Schwartz formula: eGFR (ml/min/1.73m2) = (height cm x 0.413)/ serum creatinine (mg/dl) eGFR (ml/min/1.73m2)= (height cm x 36.2/serum creatinine (µmol/l) For neonates and infants below 1 year of age, expert advice should be sought as the revised Schwartz formula is not applicable to them. Orientative dosing recommendations for the paediatric population are shown in table below that follow the same principles as in adult patients. and the addition of a glomerula filtration rate table" under this section.	12-May-20	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Vancomycin	Vancomycin	Posology and administration	Modification of text to read" Hepatic impairment No dose adjustment is needed in patients with hepatic insufficiency. " under this section. Addition of text to read "Pregnancy Significantly increased doses may be required to achieve therapeutic serum concentrations in pregnant women (see section 4.6). " under this section. Modification of text to read "Obese patients In obese patients, the initial dose should be individually adapted according to total body weight as in non-obese patients. Monitoring of vancomycin serum concentrations - The frequency of therapeutic drug monitoring (TDM) needs to be individualised based on the clinical situation and response to treatment, ranging from daily sampling that may be required in some hemodynamically unstable patients to at least once weekly in stable patients showing a treatment response. In patients with normal renal function, the serum concentration of vancomycin should be monitored on the second day of treatment immediately prior to the next dose. In patients on intermittent haemodialysis, vancomycin levels should be usually obtained before the start of the haemodialysis session. Therapeutic trough (minimum) vancomycin blood levels should normally be 10-20 mg/l, depending on the site of infection and susceptibility of the pathogen. Trough values of 15-20 mg/l are usually recommended by clinical laboratories to better cover susceptible-classified pathogens with MIC ≥1 mg/l (see sections 4.4 and 5.1). Model-based methods may be useful in the prediction of individual dose requirements to reach an adequate AUC. The model-based approach can be used both in calculating the personalised starting dose and for dose adjustments based on TDM results (see section 5.1). " under this section. Addition of text to read "Method of administration -Intravenous administration Intravenous vancomycin is usually administered as an intermittent infusion and the dosing recommendations presented in this section for the intravenous route correspond to this type of administration." under this section. Modification of text to read "Vancomycin shall only be administered as slow intravenous infusion of at least one hour duration or at a maximum rate of 10 mg/min (whichever is longer) which is sufficiently diluted (at least 100 ml per 500 mg or at least 200 ml per 1000 mg) (see section4.4). Patients whose fluid intake must be limited can also receive a solution of 500 mg/50 ml or 1000 mg/100 ml, although the risk of infusion-related undesirable effects can be increased with these higher concentrations. For information about the preparation of the solution, please see section 6.6. " under this section. Addition of text to read "Continuous vancomycin infusion may be considered, e.g., in patients with unstable vancomycin clearance. " under this section.	12-May-20	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Vancomycin	Vancomycin	Contraindications	Modification of text to read "Hypersensitivity to the active substance or to any of the excipients (see section 4.4). Vancomycin should not be administered intramuscularly due to the risk of necrosis at the site of administration. " under this section.	12-May-20	Sandoz
			Special warnings and precautions for use	Addition of text to read "Hypersensitivity reactions Serious and occasionally fatal hypersensitivity reactions are possible (see sections 4.3 and 4.8). In case of hypersensitivity reactions, treatment with vancomycin must be discontinued immediately and the adequate emergency measures must be initiated." under this section. Modification of text to read "In patients receiving vancomycin over a longer-term period or concurrently with other medications which may cause neutropenia or agranulocytosis, the leukocyte count should be monitored at regular intervals. All patients receiving vancomycin should have periodic haematologic studies, urine analysis, liver and renal function tests. Vancomycin should be used with caution in patients with allergic reactions to teicoplanin, since cross hypersensitivity, including fatal anaphylactic shock, may occur. " under Hypersensitivity reactions. Addition of text to read" Spectrum of antibacterial activity-Vancomycin has a spectrum of antibacterial activity limited to Gram-positive organisms. It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a high suspicion that the most likely pathogen(s) would be suitable for treatment with vancomycin. The rational use of vancomycin should take into account the bacterial spectrum of activity, the safety profile and the suitability of standard antibacterial therapy to treat the individual patient." under this section.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Vancomycin	Vancomycin	Special warnings and precautions for use	Modification of text to read "Ototoxicity-Ototoxicity, which may be transitory or permanent (see section 4.8) has been reported in patients with prior deafness, who have received excessive intravenous doses, or who receive concomitant treatment with another ototoxic active substance such as an aminoglycoside. Vancomycin should also be avoided in patients with previous hearing loss. Deafness may be preceded by tinnitus. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment. To reduce the risk of ototoxicity, blood levels should be determined periodically and periodic testing of auditory function is recommended. The elderly are particularly susceptible to auditory damage. Monitoring of vestibular and auditory function in the elderly should be carried out during and after treatment. Concurrent or sequential use of other ototoxic substances should be avoided. Infusion-related reactions-Rapid bolus administration (i.e. over several minutes) may be associated with exaggerated hypotension (including shock and, rarely, cardiac arrest), histamine like responses and maculopapular or erythematous rash (“red man’s syndrome” or “red neck syndrome”). Vancomycin should be infused slowly in a dilute solution (2.5 to 5.0 mg/ml) at a rate no greater than 10 mg/min and over a period not less than 60 minutes to avoid rapid infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions. The frequency of infusion-related reactions (hypotension, flushing, erythema, urticaria and pruritus) increases with the concomitant administration of anaesthetic agents (see section 4.5). This may be reduced by administering vancomycin by infusion over at least 60 minutes, before anaesthetic induction." under this section. Addition of text to read"Severe bullous reactions- Stevens-Johnson syndrome (SJS) has been reported with the use of vancomycin (see section 4.8). If symptoms or signs of SJS (e.g. progressive skin rash often with blisters or mucosal lesions) are present, vancomycin treatment should be discontinued immediately and specialised dermatological assessment be sought. " under this section. Modification of text to read "Administration site related reactions- Pain and thrombophlebitis may occur in many patients receiving intravenous vancomycin and are occasionally severe. The frequency and severity of thrombophlebitis can be minimised by administering the medicinal product slowly as a dilute solution (see section 4.2) and by changing the sites of infusion regularly." under this section.	12-May-20	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Vancomycin	Vancomycin	Special warnings and precautions for use	Addition of text to read "The efficacy and safety of vancomycin has not been established for the intrathecal, intralumbar and intraventricular routes of administration. Nephrotoxicity- Vancomycin should be used with care in patients with renal insufficiency, including anuria, as the possibility of developing toxic effects is much higher in the presence of prolonged high blood concentrations. The risk of toxicity is increased by high blood concentrations or prolonged therapy. Regular monitoring of the blood levels of vancomycin is indicated in high dose therapy and longer-term use, particularly in patients with renal dysfunction or impaired faculty of hearing as well as in concurrent administration of nephrotoxic or ototoxic substances, respectively (see section 4.2). " under this section. Modification of text to read "Paediatric population- The current intravenous dosing recommendations for the paediatric population, in particular for children below 12 years of age, may lead to sub-therapeutic vancomycin levels in a substantial number of children. However, the safety of increased vancomycin dosing has not been properly assessed and higher doses than 60 mg/kg/day cannot be generally recommended. Vancomycin should be used with particular care in premature neonates and young infants, because of their renal immaturity and the possible increase in the serum concentration of vancomycin. The blood concentrations of vancomycin should therefore be monitored carefully in these children. Concomitant administration of vancomycin and anaesthetic agents has been associated with erythema and histamine-like flushing in children. Similarly, concomitant use with nephrotoxic agents such as aminoglycoside antibiotics, NSAIDs (e.g., ibuprofen for closure of patent ductus arteriosus) or amphotericin B is associated with an increased risk of nephrotoxicity (see section 4.5) and therefore more frequent monitoring of vancomycin serum levels and renal function is indicated. " under this section.	12-May-20	Sandoz
				Additiontion of text to read " Drug interactions with anaesthetic agents- Anaesthetic induced myocardial depression may be enhanced by vancomycin. During anaesthesia, doses must be well diluted and administered slowly with close cardiac monitoring. Position changes should be delayed until the infusion is completed to allow for postural adjustment (see section 4.5). Pseudomembranous enterocolitis- In case of severe persistent diarrhoea the possibility of pseudomembranous enterocolitis that might be life-threatening has to be taken into account (see section 4.8). Anti-diarrhoeic medicinal products must not be given." under this section. Deletion of text "Doses should be titrated on the basis of serum levels. Blood levels should be monitored and renal function tests performed regularly. Patients with borderline renal function and individuals over the age of 60 should be given serial tests of auditory function and of vancomycin blood levels. " under this section.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Vancomycin	Vancomycin	Undesirable effects	Modification of text to read " The most common adverse reactions are phlebitis, pseudoallergic reactions and flushing of the upper body (“red-neck syndrome”) in connection with too rapid intravenous infusion of vancomycin." under Summary of the safety profile. Reclassification of adverse reactions as follows: Pancytopenia and Reversible neutropenia as Rare under Blood and Lypmhatic system disorder. Vertigo as Rare under Ear and labyrinth disorders. Dyspnoea as Common under Respiratory, thoracic and mediastinal disorders. Vomiting, diarrhoea as Not known under Gastrointestinal disorders. Flushing of the upper body (“red man syndrome”), pruritus, urticaria as Common under Skin and subcutaneous tissue disorders. Eosinophilia and systemic symptoms (DRESS syndrome), AGEP (acute generalised exanthematous pustulosis) as Not known under Skin and subcutaneous tissue disorders. Acute tubular necrosis as Not known under Renal and urinary disorders. Muscle spasm of the chest and back muscles as Rare under General disorders and administration site conditions. Addition of text to read "Description of selected adverse drug reactions Reversible neutropenia usually starting one week or more after onset of intravenous therapy or after total dose of more than 25 g. Intravenous vancomycin should be infused slowly." under this section.	12-May-20	Sandoz
				Modification of text to read "During or shortly after rapid infusion anaphylactic/anaphylactoid reactions including wheezing may occur. The reactions abate when administration is stopped, generally between 20 minutes and 2 hours. Vancomycin should be infused slowly (see sections 4.2 and 4.4). " under this section. Addition of text to read"Necrosis may occur after intramuscular injection. Tinnitus, possibly preceding onset of deafness, should be regarded as an indication to discontinue treatment." under this section. Modification of text to read "Ototoxicity has primarily been reported in patients given high doses, or in those on concomitant treatment with other ototoxic medicinal product like aminoglycoside, or in those who had a preexisting reduction in kidney function or hearing." under this section. Addition of text to read "If a bullous disorder is suspected, the medicinal product should be discontinued and specialised dermatological assessment should be carried out. Paediatric population- The safety profile is generally consistent among children and adult patients. Nephrotoxicity has been described in children, usually in association with other nephrotoxic agents such as aminoglycosides."	12-May-20	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Vancomycin	Vancomycin	Pharmacodynamic properties	Modification of text to read "Mechanism of action Vancomycin is a tricyclic glycopeptide antibiotic that inhibits the synthesis of the cell wall in sensitive bacteria by binding with high affinity to the D-alanyl-D-alanine terminus of cell wall precursor units. The active substance is slowly bactericidal for dividing microorganisms." under the this section. Addition of text to read "Pharmacokinetic/ pharmacodynamic relationship- Vancomycin displays concentration-independent activity with the area under the concentration curve (AUC) divided by the minimum inhibitory concentration (MIC) of the target organism as the primary predictive parameter for efficacy. On basis of in vitro, animal and limited human data, an AUC/MIC ratio of 400 has been established as a PK/PD target to achieve clinical effectiveness with vancomycin. To achieve this target when MICs are ≥1.0 mg/l, dosing in the upper range and high trough serum concentrations (15-20 mg/l) are required (see section 4.2). " under this section. MOdification of text to read "Mechanism of resistance Acquired resistance to glycopeptides is most common in enterococci and is based on acquisition of various van gene complexes which modifies the D-alanyl-D-alanine target to Dalanyl-D-lactate or D- alanyl-D-serine which bind vancomycin poorly." under this section. Addition of text "Also, methicillin- resistant staphylococcus strains (MRSA) with reduced susceptibility for vancomycin were reported. The reduced susceptibility or resistance to vancomycin in Staphylococcus is not well understood. Several genetic elements and multiple mutations are required. " under this section. Addition of text "Susceptibility testing breakpoints- Vancomycin is active against gram-positive bacteria, such as staphylococci, streptococci, enterococci, pneumococci, and clostridia. Gram-negative bacteria are resistant." under this section. Addition of This information only provides approximate guidance on the chance whether micro-organisms are susceptible to vancomycin. " under this section. Modification of "Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Susceptible species tables" under this section.	12-May-20	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Vancomycin	Vancomycin	Pharmacokinetic properties	Addition of text to read "Absorption -Vancomycin is administered intravenously for the treatment of systemic infections. In the case of patients with normal renal function, intravenous infusion of multiple doses of 1g vancomycin (15 mg/kg) for 60 minutes produces approximate average plasma concentrations of 50-60 mg/l, 20-25 mg/l and 5-10 mg/l, immediately, 2 hours and 11 hours after completing the infusion, respectively. The plasma levels obtained after multiple doses are similar to those achieved after a single dose. " under this section. Modification of text to read "Distribution -The volume of distribution is about 60 l/1.73 m2 body surface. At serum concentrations of vancomycin of 10 mg/l to 100 mg/l, the binding of the active substance to plasma proteins is approximately 30-55%, measured by ultra-filtration. Vancomycin diffuses readily across the placenta and is distributed into cord blood. In non-inflamed meninges, vancomycin passes the blood-brain barrier only to a low extent. Biotransformation -There is very little metabolism of the active substance. After parenteral administration it is excreted almost completely as microbiologically active substance (approx. 75-90% within 24 hours) through glomerular filtration via the kidneys. Elimination-The elimination half-life of vancomycin is 4 to 6 hours in patients with normal renal function and 2.2-3 hours in children. Plasma clearance is about 0.058 l/kg/h and kidney clearance about 0.048 l/kg/h. In the first 24 hours, approximately 80 % of an administered dose of vancomycin is excreted in the urine through glomerular filtration. Renal dysfunction delays the excretion of vancomycin. In anephric patients, the mean half-life is 7.5 days. Due to ototoxicity of vancomycin therapy-adjuvant monitoring of the plasma concentrations is indicated in such cases. " under this section.	12-May-20	Sandoz

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Vancomycin	Vancomycin	Pharmacokinetic properties	Addition of text to read "Although the vancomycin is not eliminated efficiently by haemodialysis or peritoneal dialysis, there have been reports of an increase in vancomycin clearance with haemoperfusion and haemofiltration. Linerarity/non-linearity Vancomycin concentration generally increases proportionally with increasing dose. Plasma concentrations during multiple dose administration are similar to those after the administration of a single dose. Characteristics in specific groups Renal impairment Vancomycin is primarily cleared by glomerular filtration. In patients with impaired renal function the terminal elimination half- life of vancomycin is prolonged and the total body clearance is reduced. Subsequently, optimal dose should be calculated in line with dosing recommendations provided in section 4.2. Hepatic impairment Vancomycin pharmacokinetics is not altered in patients with hepatic impairment. Pregnant women Significantly increased doses may be required to achieve therapeutic serum concentrations in pregnant women (see section 4.6). Overweight patients Vancomycin distribution may be altered in overweight patients due to increases in volume of distribution, in renal clearance and possible changes in plasma protein binding. In these subpopulations vancomycin serum concentration were found higher than expected in male healthy adults (see section 4.2). Paediatric population Vancomycin PK has shown wide inter-individual variability in preterm and term neonates. In neonates, after intravenous administration, vancomycin volume of distribution varies between 0.38 and 0.97 l/kg, similar to adult values, while clearance varies between 0.63 and 1.4 ml/kg/min. Half-life varies between 3.5 and 10 h and is longer than in adults, reflecting the usual lower values for clearance in the neonate. In infants and older children, the volume of distribution ranges between 0.26-1.05 l/kg while clearance varies between 0.331.87 ml/kg/min.	12-May-20	Sandoz