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	Actrapid	Insulin human, rDNA	Posology and method of administration	Revision of texts under administration to read "Actrapid® is administered subcutaneously by injection in the abdominal wall. If convenient, the thigh, the gluteal region or the deltoid region may also be used. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis."	5-Oct-21	Novonordisk
			Special warnings and precautions for use	Addition of texts to read "Skin and subcutaneous tissue disorders: Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered."		
			Undesirable effects	Addition of texts under skin and subcutaneous tissue disorders to read "Not known – Cutaneous amyloidosis"		
				Revision of texts to read "Skin and subcutaneous tissue disorders: Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.		
2	Adriblastina	Doxorubicin Hydrochloride	Special warnings and precautions for use	Addition of text to read " Embryo-fetal Toxicity- Doxorubicin can cause genotoxicity. An effective method of contraception is required for both male and female patients during and for a period after treatment with doxorubicin. Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available (see Sections 4.6 and 5.3)."	27-Oct-21	Pfizer

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Adriblastina	Doxorubicin Hydrochloride	Fertility, pregnancy and lactation	Revision of text " In men, doxorubicin is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent; however, sperm counts have been reported to return to normospermic levels in some instances. This may occur several years after the end of therapy. Men undergoing doxorubicin treatment should use effective contraceptive methods. Both men and women should seek advice on fertility preservation before treatment." under Impairment of Fertility. Addition of text "Women of Childbearing Potential/Contraception in Males and Females- Women of childbearing potential should be advised to avoid becoming pregnant during treatment and to use effective contraceptive methods during treatment and for at least 6 months and 10 days after last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with doxorubicin and for at least 3 months and 10 days after last dose. Revision of text "Lactation- Doxorubicin is excreted in breast milk (see Section 5.2). Because of the potential for serious reactions in nursing infants from doxorubicin women should not breastfeed while undergoing treatment with doxorubicin and for at least six months and 10 days after last dose."	27-Oct-21	Pfizer
			Nature and contents of container	Addition of text " Not all strength may be marketed."		
3	Aromasin	Exemestane	Undesirable effects	Revision and addition of table 1 to include System Organ Class (SOC) and the reported adverse drug reactions within the SOCs	5-Oct-21	Pfizer
				Addition of texts under musculoskeletal and connective tissue disorders to include "Trigger finger and Tenosynovitis stenosans".		
4	Brilinta	Ticagrelor	Special warnings and precautions for use	Revision of text to read "Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders, active or recent gastrointestinal bleeding) or who are at increased risk of trauma. The use of ticagrelor is contraindicated in patients with active pathological bleeding, in those with a history of intracranial haemorrhage, and in patients with severe hepatic impairment (see section 4.3) " under Bleeding risk	7-Dec-21	AstraZeneca UK Limited
			Undesirable effects	Revision of text to read "Intracranial haemorrhagem i.e. spontaneous, procedure related or traumatic intracranial haemorrhage" in Table 1 - Adverse reactions by frequency and system organ class (SOC)		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Celebrex	Celecoxib	Special warnings and precautions for use	Deletion of text "Systemic onset JIA. NSAIDs including celecoxib should be used only with caution in patients with systemic-onset JIA, due to the risk of disseminated intravascular coagulation. Patients receiving celecoxib who have systemic-onset JIA should be monitored for the development of abnormal coagulation tests".	13-Dec-21	Pfizer
			Fertility, pregnancy and lactation	Revision of text to read "Such effects may occur shortly after treatment initiation and are usually reversible upon discontinuation" under Pregnancy.		
			Undesirable effects	Deletion of text "Generally, the adverse reactions observed in the pivotal ediatric study were similar to those observed in adult arthritis studies (see Table 1 and Section 5.1 Pharmacodynamic properties, JIA). Additionally, the following adverse reactions are not listed in Table 1 and were attributed by the investigator in the pivotal pediatric study as possibly related to treatment with celecoxib: headache (11.3%, very common), exacerbation of hematuria (reported as exacerbation of hematuria, 0.6%, uncommon) and asthma 1 patient who had controlled asthma at baseline] (0.6%, uncommon). Compared to naproxen, celecoxib at doses of 3 mg/kg and 6 mg/kg twice daily had no observable deleterious effect on growth and development during the course of the 12-week double-blind study" under Pediatric Population.		
			Pharmacodynamic properties	Deletion of text to read "The efficacy and safety of celecoxib for JIA have not been studied beyond 6 months. The long-term CV toxicity in children exposed to celecoxib has not been evaluated and it is unknown if the long-term risk may be similar to that seen in adults exposed to celecoxib or other COX-2 selective and non-selective NSAIDs (see Section 4.4 Special warnings and precautions for use, Cardiovascular Effects)" under Clinical Studies, subheading Juvenile Idiopathic Arthritis (JIA).		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	Co-Micardis	Telmisartan and Hydrochlorothiazide	Dosage and Administration	Addition of text "Sodium or volume depletion should be corrected before treatment commencement with Micardis PLUS" under Adults. Deletion of text "MICARDIS PLUS may be taken with or without food" under Adults. Revision of text to read "Due to the hydrochlorothiazide component, MICARDIS PLUS must not be used in patients with severe renal dysfunction (creatinine clearance < 30 mL/min). Loop diuretics are preferred to thiazides in this population. Experience in patients with mild to moderate renal impairment is modest but has not suggested adverse renal effects and dose adjustment is not considered necessary. Periodic monitoring of renal function is advised" under Renal Impairment Revision of text to read "In patients with mild to moderate hepatic impairment the posology should not exceed MICARDIS PLUS 40/12.5 mg once daily. MICARDIS PLUS is not contraindicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function " under Hepatic impairment. Revision of text to read "No dosage adjustment is necessary. With advanced age (≥ 65 years), one should be aware of possible renal impairment" under Elderly. Addition of text "Use of MICARDIS PLUS is not recommended in children and adolescents" under Children and adolescents. Addition of text " MICARDIS PLUS may be taken with or without food" under Method of Administration.	6-Dec-21	Boehringer Ingelheim Group of Companies

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	Co-Micardis	Telmisartan and Hydrochlorothiazide	Contraindications	Revision of text to read " Hypersensitivity to the active ingredient, to any of the excipients, or to other sulphonamide derived substances (hydrochlorothiazide is a sulphonamide-derived substance); Pregnancy; Lactation; Choleastasis and biliary obstructive disorders; Severe hepatic impairment, coma hepatricum, hepatic precoma; Severe renal impairment (creatinine clearance < 30 mL/min) or serum creatinine > 1.8 mg/100 ml), anuria, or acute glomerulonephritis; Refractory hypokalaemia, hypercalcaemia; Therapy-refractory hyponatraemia; Hypovolaemia; Symptomatic hyperuricaemia/gout; The concomitant use of MICARDIS PLUS with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2 " Deletion of the text "In case of rare hereditary conditions that may be incompatible with an excipient of the product the use of the product is contraindicated (please refer tosee Section "Special warnings and precautions")".	6-Dec-21	Boehringer Ingelheim Group of Companies
			Special Warning and Precations	Revision of text under subsection Hepatic impairment to read as "MICARDIS PLUS must not be given to patients with cholestasis, biliary obstructive disorders or severe hepatic insufficiency since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan. MICARDIS PLUS should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with MICARDIS PLUS in patients with hepatic impairment". Revision of text to read "Choroidal effusion, Acute Myopia and Secondary Angle-Closure Glaucoma. Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy" under Choroidal effusion, Acute Myopia and Secondary Angle-Closure Glaucoma		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	Co-Micardis	Telmisartan and Hydrochlorothiazide	Use in Specific Populations	Revision of text to read " Non-clinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity" under Pregnancy Revision of text to read " MICARDIS PLUS is contraindicated during lactation since it is not known whether telmisartan is excreted in human milk. Non-clinical studies have shown excretion of telmisartan in breast milk" under lactation. Addition of text "The ability to drive or work without suitable safeguards may be impaired" under Driving and using Machines.	6-Dec-21	Boehringer Ingelheim Group of Companies

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	Co-Micardis	Telmisartan and Hydrochlorothiazide	Interactions	Addition of text " Interactions linked to telmisartan ". Revision of text to read " Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) including ASA at anti inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the Renin-Angiotensin-System like telmisartan may have synergistic effects. Patients receiving NSAID and telmisartan should be adequately hydrated and be monitored for renal function at the beginning of combined treatment" under Interaction linked to telmisatan. Addition of text "Interactions linked to hydrochlorothiazide (HCT)". Addition of text " The antihypertensive effect of HCT can be potentiated by other diuretics, antihypertensive agents, guanethidine, methyldopa, calcium antagonists, ACE inhibitors, ARBs, DRIs, betareceptor blockers, nitrates, barbiturates, phenothiazines, tricyclic antidepressants, vasodilators or by alcohol consumption. Salicylates and other non-steroidal anti-inflammatory drugs (e.g. indomethacin) may reduce the antihypertensive and diuretic effect of HCT. In patients taking high-dose salicylates, the toxic effect of salicylates on the central nervous system may be potentiated. In patients developing hypovolaemia during treatment with HCT, concomitant administration of non-steroidal antiinflammatory drugs may trigger acute renal failure. Co-administration of thiazides (including hydrochlorothiazide) and allopurinol may possibly increase the frequency of hypersensitivity reactions to allopurinol. Co-administration of thiazides and amantadine may possibly increase the risk of amantadinerelated adverse reactions. There is an increased risk for the onset of hyperglycaemia with concomitant administration of HCT and beta-receptor blockers. The effect of insulin or oral antidiabetics, uric acid-lowering agents, as well as norepinephrine and epinephrine, may be attenuated with concomitant use of HCT. An adjustment of the insulin or oral antidiabetic dosage may therefore be required. In concomitant treatment with cardiac glycosides, it must be remembered that myocardial sensitivity to cardiac glycosides will be increased by any hypokalaemia and/or hypomagnesaemia that develops during HCT therapy, thereby potentiating the effects and adverse effects of these cardiac glycosides. Concomitant use of HCT and kaliuretic diuretics (e.g. furosemide), glucocorticoids, ACTH, carbenoxolone, penicillin	6-Dec-21	Boehringer Ingelheim Group of Companies

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	Co-Micardis	Telmisartan and Hydrochlorothiazide	Adverse Reactions	Revision of text to read "Adverse reactions not observed in clinical trials with telmisartan plus hydrochlorothiazide but expected during treatment with MICARDIS PLUS based on the experience with telmisartan or hydrochlorothiazide alone are shown in the table below classified by MedDRA System organ class and MedDRA Preferred Terms" under Tabulated summary of adverse reactions. Addition of table under Tabulated summary of adverse reactions. Deletion of the texts " (including cystitis), sialadenitis" under the MedDRA System Organ Class terminology, Infections and infestations. Addition of the adverse reaction "cystitis" under the MedDRA System Organ Class terminology, Infections and infestations. Addition of the adverse reactions " basal cell carcinoma" under the MedDRA System Organ Class terminology, Neoplasms benign, malignant and unspecified (incl cysts and polys). Deletion of the adverse reactions "Non-melanoma skin cancer and squamous cell carcinoma of skin or lip" under the MedDRA System Organ Class terminology, Neoplasms benign, malignant and unspecified (incl cysts and polys). Addition of the adverse reactions "thrombocytopenic purpura" under the MedDRA System Organ Class terminology, Blood and lymphatic system disorders. Deletion of the text "(sometimes with purpura), neutropenia" under the MedDRA System Organ Class terminology, Blood and lymphatic system disorders. Revision of the text to read "bone marrow failure" under the MedDRA System Organ Class terminology, Blood and lymphatic system disorders. Addition of the adverse reactions "vasculitis necrotising " under the MedDRA System Organ Class terminology, Immune system disorders. Deletion of the text "exacerbation or activation of systemic, allergy" under the MedDRA System Organ Class terminology, Immune system disorders.	6-Dec-21	Boehringer Ingelheim Group of Companies
			Pharmacokinetics	Addition of the text "PK in specific populations". Addition of the text "In patients of more advanced age, one should be aware of possible renal impairment" under PK in specific populations. Deletion of the text "Paediatric population. No pharmacokinetic data for Micardis® Plus are available in the paediatric population" under PK in specific populations		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Dalacin C	Clindamycin	Clinical Pharmacology	Addition of texts under special population to include "Dosage schedules do not need to be modified in patients with renal disease."	7-Oct-21	Pfizer
			Special warnings and precautions for use	Addition of texts to include "Renal Toxicity: is potentially nephrotoxic. Acute kidney injury including acute renal failure has been reported. Therefore, monitoring of renal function should be considered during therapy of patients with pre-existing renal dysfunction or taking concomitant nephrotoxic drugs and monitoring of renal function should be performed if therapy is prolonged."		
			Undesirable effects	Revision of texts to read "Acute Kidney Injury: Signs of renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria have been observed".		
8	Diflucan	Fluconazole	Special warnings and precautions for use	Revision of text to read " Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported. AIDS patients are more prone to the development of severe cutaneous reactions to many medicinal products. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, further therapy with this medicinal product should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely, and fluconazole discontinued if bullous lesions or erythema multiforme develop." under sub-heading Dermatological reactions. Addition of text " Studies have shown an increasing prevalence of infections with Candida species other than C. albicans. These are often inherently resistant (e.g. C. krusei and C. auris) or show reduced susceptibility to fluconazole (C. glabrata). Such infections may require alternative antifungal therapy secondary to treatment failure. Therefore, prescribers are advised to take into account the prevalence of resistance in various Candida species to fluconazole." under sub-heading Candidiasis.	2-Dec-21	Pfizer
			Interaction with other medicinal products and other forms of interaction	Addition of text " Tolvaptan- Exposure to tolvaptan is significantly increased (200% in AUC; 80% in Cmax) when tolvaptan, a CYP3A4 substrate, is co-administered with fluconazole, a moderate CYP3A4 inhibitor, with risk of significant increase in adverse reactions particularly significant diuresis, dehydration and acute renal failure. In case of concomitant use, the tolvaptan dose should be reduced as instructed in the tolvaptan prescribing information and the patient should be frequently monitored for any adverse reactions associated with tolvaptan. " under sub-heading Concomitant use of the following other medicinal products lead to precautions and dose adjustments		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
8	Diflucan	Fluconazole	Fertility, pregnancy and lactation	Addition of text " Data from several thousand pregnant women treated with a cumulative dose of ≤ 150 mg of fluconazole, administered in the first trimester, show no increase in the overall risk of malformations in the foetus. In one large observational cohort study, first trimester exposure to oral fluconazole was associated with a small increased risk of musculoskeletal malformations, corresponding to approximately 1 additional case per 1000 women treated with cumulative doses ≤ 450 mg compared with women treated with topical azoles and to approximately 4 additional cases per 1000 women treated with cumulative doses over 450 mg. The adjusted relative risk was 1.29 (95% CI 1.05 to 1.58) for 150 mg oral fluconazole and 1.98 (95% CI 1.23 to 3.17) for doses over 450 mg fluconazole." under sub-heading Pregnancy.	2-Dec-21	Pfizer
			Undesirable effects	Addition of text " Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment (see section 4.4)." under Summary of safety profile		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
8	Diflucan	Fluconazole	Pharmacodynamic properties	Revision of text to read " *In vitro* , fluconazole displays antifungal activity against clinically common *Candida* species (including *C. albicans, C. parapsilosis, C. tropicalis). C. glabrata* shows reduced susceptibility to fluconazole while *C. krusei* and *C. auris* are resistant to fluconazole. The MICs and epidemiological cut-off value (ECOFF) of fluconazole for *C. guilliermondii* are higher than for *C. albicans* ." under Susceptibility in vitro. Addition of text " In usually susceptible species of Candida, the most commonly encountered mechanism of resistance development involves the target enzymes of the azoles, which are responsible for the biosynthesis of ergosterol. Resistance may be caused by mutation, increased production of an enzyme, drug efflux mechanisms, or the development of compensatory pathways." under Mechanisms of resistance. Revision of text to read " There have been reports of superinfection with Candida species other than C. albicans, which often have inherently reduced susceptibility (C. glabrata) or resistance to fluconazole (e.g. C. krusei, C. auris). Such infections may require alternative antifungal therapy. The resistance mechanisms have not been completely elucidated in some intrinsically resistant (C. krusei) or emerging (C. auris) species of Candida. EUCAST Breakpoints Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility in vitro and clinical response EUCAST-AFST (European Committee on Antimicrobial Susceptibility Testing-Subcommitte on Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for Candida species (EUCAST Fluconazole rationale document (2020)-version 3; European Committee on Antimicrobial Susceptibility Testing, Antifungal Agents, Breakpoint tables for interpretation of MICs, Version 10.0, valid from 2020-02-04). These have been divided into non-species related breakpoints; which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:" Addition of a key " * = The entire C. glabrata is in the I category. MICs against C. glabrata should be interpreted as resistant when above 16 mg/L. Susceptible category (≤0.001 mg/L) is simply to avoid misclassification of "I" strains as "S" strains. I - Susceptible, increased exposure: A microorganism is categorised as Susceptible, increased exposure when there is a high likelihood of therapeutic success because	2-Dec-21	Pfizer
			Preclinical safety data	Revision of text to read " Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5, or 10 mg/kg/day (approximately 2-7 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas." under Carcinogenesis.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
8	Diflucan	Fluconazole	Shelf life	Revision of text to read " Do not use Diflucan after the expiry date which is stated on the carton/blister after « EXP »: The expiry date refers to the last day of that month."	2-Dec-21	Pfizer
9	Feldene	Piroxicam	Special warnings and precautions for use	Addition of texts under skin reactions to include " Cases of fixed drug eruption (FDE) have been reported with piroxicam. Piroxicam should not be reintroduced in patients with history of piroxicam-related FDE. Potential cross reactivity might occur with other oxicams. "	22-Sep-21	Pfizer
			Undesirable effects	Addition of texts under Cutaneo-mucous reactions to include "fixed drug eruption have been reported- frequency unknown".		
			Pharmacological properties	Addition of texts under Pharmacokinetics (Absorption) to read "The global bioavailability and significance of the absorption are not modified baby food, with the latter slightly slowing the absorption rate."		
10	Implanon	Etonogestrel implant	Special warnings and precautions for use	Revision of texts to read "In situ broken or bent implant There have been reports of broken or bent implants, which may be due to external forces applied while in the patient's arm. There have also been reports of migration of a broken implant fragment within the arm. However, when an implant is broken, it should be removed, and it is important to remove it in its entirety. Refer to section 4.2 for the procedures of implant removal (either palpable or non- palpable)."	18-Oct-21	MSD
11	Insulatard	Isophane Insulin human	Posology and method of administration	Revision of texts under administration to read "Insulatard is administered subcutaneously by injection in the thigh. If convenient, the abdominal wall, gluteal region or the deltoid region may also be used. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis."	5-Oct-21	Novonordisk
			Special warnings and precautions for use	Addition of texts to read "Skin and subcutaneous tissue disorders: Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered."		
			Undesirable effects	Addition of texts under skin and subcutaneous tissue disorders to read "Not known – Cutaneous amyloidosis"		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
11	Insulatard	Isophane Insulin human	Undesirable effects	Revision of texts to read "Skin and subcutaneous tissue disorders: Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.	5-Oct-21	Novonordisk
12	Januvia	Sitagliptin phosphate	Dosage and Administration	Revision of text to read "JANUVIA is not effective in children and adolescents 10 to 17 years of age with type 2 diabetes. JANUVIA has not been studied in children younger than 10 years of age" under Pediatric Population.	7-Dec-21	MSD Idea Pharmaceuticals Ltd
13	Levemir	Insulin detemir	Posology and method of administration	Revision of texts to read "Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis."	5-Oct-21	Novonordisk
			Special warnings and precautions for use	Addition of texts to read "Skin and subcutaneous tissue disorders: Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered."		
			Undesirable effects	Addition of texts under skin and subcutaneous tissue disorders to read "Not known – Cutaneous amyloidosis"		
				Revision of texts to read "Skin and subcutaneous tissue disorders: Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions."		
14	Mixtard	Insulin human (rDNA)	Posology and method of administration	Revision of texts under administration to read "Mixtard is administered subcutaneously by injection in the thigh or abdominal wall. If convenient, the gluteal region or the deltoid region may also be used. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis."	5-Oct-21	Novonordisk

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
14	Mixtard	Insulin human (rDNA)	Special warnings and precautions for use	Addition of texts to read "Skin and subcutaneous tissue disorders: Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered."	5-Oct-21	Novonordisk
			Undesirable effects	ddition of texts under skin and subcutaneous tissue disorders to read "Not known – Cutaneous amyloidosis"		
				Revision of texts to read "Skin and subcutaneous tissue disorders: Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions."		
15	Novomix	Insulin aspart	Posology and method of administration	Revision of texts to read "Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis."	5-Oct-21	Novonordisk
			Special warnings and precautions for use	Addition of texts to read "Skin and subcutaneous tissue disorders: Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered."		
			Undesirable effects	Addition of texts under skin and subcutaneous tissue disorders to read "Not known – Cutaneous amyloidosis"		
				Revision of texts to read "Skin and subcutaneous tissue disorders: Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions."		
16	Novorapid	Insulin aspart	Posology and method of administration	Revision of texts to read "Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis."	5-Oct-21	Novonordisk

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
16	Novorapid	Insulin aspart	Special warnings and precautions for use	Addition of texts to read "Skin and subcutaneous tissue disorders: Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered."	5-Oct-21	Novonordisk
			Undesirable effects	Addition of texts under skin and subcutaneous tissue disorders to read "Not known – Cutaneous amyloidosis"		
				Revision of texts to read "Skin and subcutaneous tissue disorders: Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions."		
17	Pasurta	Erenumab	Composition	Deletion of text "70 mg Erenumab in 1.0 mL (70 mg/mL) solution, 70 mg/mL solution for injection in a pre-filled syringe, subcutaneous use. 140 mg Erenumab in 1.0 mL (140 mg/mL) solution. 140 mg/mL solution for injection in a pre-filled syringe, subcutaneous use. Not all dosage forms may be available in all countries." under Pharmaceutical forms. Addition of text" (genetically engineered using Chinese hamster ovary cells)" under Active substance. Revision of text to read "Sucrose, polysorbate 80, sodium hydroxide equivalent to 0.2 mg sodium/ml, glacial acetic acid, water for injections" under Excipients. Addition of text "Solution for injection in pre-filled syringe or pre-filled pen for subcutaneous use: 1 pre-filled syringe or 1 pre-filled pen of 1 ml contains 70 mg erenumab in 1 ml (70 mg/ml) solution for injection 1 pre-filled syringe or 1 pre-filled pen of 1 ml contains 140 mg erenumab in 1 ml (140 mg/ml) solution for injection "under Pharmaceutical form and quantity of active substance per unit.	28-Sep-21	Novartis International AG

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
17	Pasurta	Erenumab	Dosage regimen and Administration	Revision of text to read "The indication for therapy must be established by a physician with experience in migraine treatment and the patient must be monitored by this physician throughout treatment. Continuation of therapy should be re-evaluated in the event of a lack of therapeutic response or after a maximum of 12 months. To ensure traceability of medicinal products produced using biotechnology, it is recommended that the trade name and batch number be documented at every treatment. The recommended dose of Pasurta is 70 mg administered by subcutaneous injection once monthly. In patients exhibiting an inadequate response to this dosage it may be increased to 140 mg once monthly provided that this yields an improved response. Patients with hepatic impairment- No clinical studies have been performed in patients with hepatic impairment. No dose adjustment is recommended in patients with hepatic impairment as erenumab, a human immunoglobulin G, is not metabolized by cytochrome P450 enzymes and the liver is not a major pathway for its clearance. Patient with renal impairment- No dose adjustment is necessary in patients with mild to moderate renal impairment. Population pharmacokinetic analysis of integrated data from the Pasurta clinical trials showed no difference between patients with mild or moderate renal impairment and those with renal function with regard to the pharmacokinetics of erenumab. Patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2) have not been studied. Elderly patients- Clinical studies did not include sufficient numbers of patients aged 65 and over to determine whether such patients respond differently from younger patients. A dose adjustment is not required as the pharmacokinetics of erenumab are not affected by age. Children and adolescents-The safety and effectiveness of Pasurta has not been studied in pediatric patients. Pasurta must therefore not be used in this group. Late administration-If a scheduled dose is forgotten, it should be administered as soon as possible and further injections should be scheduled monthly from the date of the last injection. Method of administration- Pasurta is intended for patient self-administration into the abdominal wall or thigh. Injection sites should be rotated and injections should not be	28-Sep-21	Novartis International AG
			Contraindications	Revision of text to read "hypersensitivity to the active substance erenumab or any of the excipients listed under "Composition" ".		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
17	Pasurta	Erenumab	Warnings and Precautions	Revision of text to read "Hypersensitivity Reactions- Serious hypersensitivity reactions, including rash, angioedema, and anaphylactoid reactions, have been reported with Pasurta in post marketing setting. These reactions may occur within minutes, but some may not become apparent until more than one week after treatment. If a serious or severe hypersensitivity reaction occurs, administration of Pasurta must be discontinued immediately and appropriate therapy initiated. Constipation with severe complications- Constipation with severe complications may occur during Pasurta treatment (see "Adverse effects"). Patients taking Pasurta should therefore be monitored for signs of severe constipation and treated as clinically indicated. Co-administration of medicinal products associated with decreased gastrointestinal motility may increase the risk of severe constipation and potential complications. Patients with severe cardiovascular disorders- Patients with certain severe cardiovascular diseases were excluded from participation in the clinical studies. No safety data are available for these patients. Latex-sensitive patients- The removable cap of the Pasurta pre-filled syringe and the Pasurta pre-filled pen contains dry natural rubber latex, which may cause allergic reactions in individuals sensitive to latex. This medicine contains less than 1 mmol (23 mg) of sodium per pre-filled syringe/pre-filled pen (70 mg/ml, 140 mg/ml), making it practically "sodium-free". Interactions- In an open-label pharmacokinetic drug interaction study of Pasurta and a combined oral contraceptive in healthy female subjects erenumab (140 mg subcutaneously [s.c.], single dose) did not affect the pharmacokinetics of a combined oral contraceptive containing ethinylestradiol and norgestimate. In a randomised, double-blind, placebo-controlled study in healthy subjects co-administration of erenumab (140 mg intravenously [i.v.], single dose) and sumatriptan had no effect on resting blood pressure compared with sumatriptan alone. Pasurta had no effect on the pharmacokinetics of sumatriptan. Erenumab is not metabolised by cytochrome P450 enzymes. Therefore, interactions with concomitant medications that are substrates, inducers or inhibitors of cytochrome P450 enzymes are unlikely. Pregnancy/Breast-feeding	28-Sep-21	Novartis International AG

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
17	Pasurta	Erenumab	Adverse effects	Revision of text to read "Data from two phase 3 and two phase 2 clinical studies on migraine were pooled to evaluate the safety of Pasurta in comparison to placebo up to 12 weeks after treatment initiation. A total of 2656 patients took part in the placebo-controlled studies. 1,613 patients received Pasurta and 1,043 patients received placebo. Of these, 893 patients received 70 mg dose of Pasurta and 507 patient received 140 mg dose of Pasurta. The overall safety population, including the patient in the ongoing open label extension phase with Pasurta, comprised >2,500 patients (>2300 patient-years) who had received at least one dose of Pasurta: >2,000 patients were treated for at least 6 months and >1,200 patients were treated for at least 12 months. Frequencies are defined as follows: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), "not known" (cannot be estimated from available data). Immune system disorders- Frequency not known: Hypersensitivity reactions including rash, angioedema and anaphylactoid reactions [see section WARNINGS AND PRECAUTIONS] Gastrointestinal disorders- Common: Constipation (see "Warnings and precautions" and "Description of specific adverse effects") Skin and subcutaneous tissue disorders- Common: Pruritus Musculoskeletal and connective tissue disorders- Common: Muscle spasms General disorders and administration site conditions Common: Injection site reactions (pain, erythema or pruritus) Post-marketing adverse effects Immune system disorders- Frequency not known: Hypersensitivity reactions, including rash, angioedema and anaphylactoid reactions (see "Warnings and precautions"). Gastrointestinal disorder- Frequency not known: Cases of constipation with severe complications have been reported (see "Warnings and precautions" and "Description of specific adverse	28-Sep-21	Novartis International AG

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
17	Pasurta	Erenumab	Clinical Efficacy	Addition of text "Chronic Migraine: Study 1 (Study 20120295)- Pasurta was evaluated for prophylaxis of chronic migraine in a randomized, multi-center, 12 week, placebo-controlled, double-blind study. A total of 667 patients with a history of migraine with or without aura (≥15 headache days per month with ≥8 migraine days per month) were randomized to receive placebo (n = 286), Pasurta 70 mg (n = 191) or Pasurta 140 mg (n = 190) subcutaneous injections every 4 weeks for 12 weeks. The mean migraine frequency at baseline was approximately 18 migraine days per month and was similar across treatment groups. Patients were allowed to use acute headache treatments such as triptans, ergotamine derivatives and NSAIDs during the study. Patients had a median age of 43 years (range: 18 to 66 years), 83% were female and 94% were white. Patients with pre-existing myocardial infarction, stroke, transient ischaemic attacks, unstable angina pectoris, coronary artery bypass surgery or other revascularisation procedures within 12 months prior to screening were excluded from study 20120295. The primary outcome variable was the change in monthly migraine days from baseline at Month 3. Secondary outcome variables included the achievement of 50 to 100% reduction in monthly migraine days from baseline (≥50% responders) and change from baseline in monthly acute migraine specific medication days. Episodic Migraine: Study Study 20120296, STRIVE- Study 20120296 was a randomized, multi-center, 24-week, placebo-controlled, double- blind study evaluating Pasurta for prophylaxis of episodic migraine. A total of 955 patients with history of migraine with or without aura for a duration of ≥ 12 months and 4-14 migraine days per month were randomized to receive either Pasurta 70 mg (n=317), Pasurta 140 mg (n = 319), or placebo (n = 319) by subcutaneous injection every 4 weeks for 24 weeks. The mean migraine frequency at baseline was approximately 8 migraine days per month and was similar across treatment groups. Patients were allowed to use acute headache treatments such as triptans, ergotamine derivatives and NSAIDs during the study. The median age of the patients was 42 years (18 to 65 years),	28-Sep-21	Novartis International AG
18	Ponstan	Mefenamic acid	Fertility, pregnancy and lactation	Revision of text to read "Such effects may occur shortly after treatment initiation and are usually reversible upon discontinuation" under the heading Pregnancy.	13-Dec-21	Pfizer

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
18	Ponstan	Mefenamic acid	Special precautions for disposal and other handling	Addition of text "Keep out of the sight and reach of children". Addition of text "Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment".	13-Dec-21	Pfizer
19	Rhinaphyto Elixir	Thyme liquid extract, and primula root liquid extract	Contraindications	Revision of text to read "This medicinal product must not be used in patients with hypersensitivity to the active substances or other plants of the Lamiaceae (Labitae) family, or to any of the excipients listed in Section 6.1".	13-Dec-21	Sanofi
			Method of administration	Addition of text "There are no adequate data for specific dosage recommendations in patients with restricted kidney function or liver function".		
			Special warnings and precautions for use	Addition of text "1 ml contain 1.1 g of a mix of sucrose, glucose and fructose. This should be taken into account in patients with diabetes mellitus".		
			Fertility, pregnancy and lactation	Revision of text to read "There are no studies on the use of thyme and primrose products during pregnancy and breastfeeding. The use is therefore, Rhinaphyto not recommended" under Pregnancy and Lactation. Revision of text to read "There are no data available concerning the effect on fertility".		
			Pharmaceutical Particulars	Deletion of text "Note for patients with diabetes; 5 ml is equivalent to 0.38 white bread units. Energy value: 77 kJ = approx. 18 kcal per 5 ml".		
20	Ryzodeg	Insulin degludec a/insulin aspart	Posology and method of administration	Revision of texts to read "Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis."	5-Oct-21	Novonordisk
			Special warnings and precautions for use	Addition of texts to read "Skin and subcutaneous tissue disorders: Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered."		
			Undesirable effects	Addition of texts under skin and subcutaneous tissue disorders to read "Not known – Cutaneous amyloidosis"		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
20	Ryzodeg	Insulin degludec / insulin aspart	Undesirable effects	Revision of texts to read "Skin and subcutaneous tissue disorders: Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions."	5-Oct-21	Novonordisk
21	Tazocin	Piperacillin / Tazobactam	Special warnings and precautions for use	Addition of texts to include " Rare cases of haemophagocytic lymphohistiocytosis (HLH) have been observed following therapy (>10 days) with piperacillin tazobactam, often as a complication of DRESS. HLH is a pathologic immune activation which leads to excessive systemic inflammation and can be life threatening and early diagnosis and rapid initiation of immunosuppressive therapy is essential. Characteristic signs and symptoms include fever, hepatosplenomegaly, cytopenias, hyperferritinaemia, hypertriglyceridaemia, hypofibrinogenaemia, and haemophagocytosis. If piperacillin tazobactam is suspected as possible trigger, treatment should be discontinued."	27-Oct-21	Pfizer
22	Tresiba flextouch	Insulin degludec	Pharmacological properties	Revision of texts under pharmacological properties to read " The day-to-day variability, expressed as the coefficient of variation, in glucose-lowering effect during one dosing interval of 0-24 hours at steady state (AUCGIR,τ,SS) is 20% for insulin degludec, which is significantly lower than for insulin glargine (100 units/mL)."	5-Oct-21	Novo Nordisk
23	Vigamox	Moxifloxacin	Therapeutic Indications	Addition of text ''Consideration should be given to official guidance on the appropriate use of antibacterial agents"	13-Dec-21	Novartis International AG
			Posology and Method of Administration	Addition of text ''If no improvement is observed within 5 days of initiating therapy, the diagnosis and/or treatment should be reconsidered. The duration of treatment depends on the severity of the disorder and on the clinical and bacteriological course of infection.''		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
23	Vigamox	Moxifloxacin	Special Warnings and Precautions for Use	Addition of text ''Data are very limited to establish efficacy and safety of VIGAMOX eye drops in the treatment of conjunctivitis in neonates. Therefore, use of this medicinal product to treat conjunctivitis in neonates is not recommended'' Addition of text ''VIGAMOX eye drops should not be used for the prophylaxis or empiric treatment of gonococcal conjunctivitis, including gonococcal ophthalmia neonatorum, because of the prevalence of fluoroquinolone-resistant Neisseria gonorrhoeae. Patients with eye infections caused by Neisseria gonorrhoeae should receive appropriate systemic treatment.'' Addition of text ''The medicinal product is not recommended for the treatment of Chlamydia trachomatis in patients less than 2 years of age as it has not been evaluated in such patients. Patients older than 2 years of age with eye infections caused by Chlamydia trachomatis should receive appropriate systemic treatment.'' Addition of text to read "Neonates with ophthalmia neonatorum should receive appropriate treatment for their condition, e.g., systemic treatment in cases caused by Chlamydia trachomatis or Neisseria gonorrhoeae''.	13-Dec-21	Novartis International AG
			Undesirable Effects	Revision of text to read under the sub heading eye disorders '' Not known: endophthalmitis, ulcerative keratitis, corneal erosion, corneal abrasion, intraocular pressure increased, corneal opacity, corneal infiltrates, corneal deposits, eye allergy, keratitis, corneal oedema, lacrimation increased, photophobia, eye discharge, foreign body sensation in eyes''		
			Effects on Ability to Drive and Use Machines	Revision of text to read ''VIGAMOX eye drops has no or negligible influence on the ability to drive and use machines Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation the patient must wait until the vision clears before driving or using machinery. ''.		
			Overdose	Revision of text to read ''An ocular overdose of VIGAMOX eye drops may be flushed from the eye(s) with lukewarm water. The limited holding capacity of the conjunctival sac for ophthalmic products practically precludes any overdosing of the medicinal product Due to the characteristics of this preparation no toxic effects are to be expected with an ocular overdose of the product, or in the event of accidental ingestion of the contents of one bottle.''.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
23	Vigamox	Moxifloxacin	Pharmacological properties	Addition of text to read '' Other microorganisms: None '' under the sub-heading Species for which acquired resistance may be a problem Addition of text to read '' Other microorganisms: None '' under the sub-heading Inherently resistant organisms	13-Dec-21	Novartis International AG
			Pharmacokinetic properties	Revision of text to read “In rabbit, moxifloxacin is widely distributed into ocular tissues with the highest concentration found in the cornea after 0.5 hours. Moxifloxacin does bind to melanin, resulting in a long half-life in the iris-ciliary body (pigmented rabbit) after ocular administration.” under Distribution. Addition of text ''Drug-drug interaction studies have not been conducted with VIGAMOX eye drops. In vitro studies indicate that moxifloxacin or the N-sulfonate of moxifloxacin do not inhibit P-450 isoforms; CYP3A, CYP2D6, CYP2C9, CYP2C19 or CYP1A2. Based on observed moxifloxacin human plasma concentrations after ocular dosing, it is unlikely that drug-drug interactions will occur.'' under Metabolism.		
			Pharmaceutical Particulars	Addition of text to read "Do not store above 30°C. Do not use this medicine after the expiry date which is stated on the packaging. Discard 4 weeks after first opening'' under Special precautions for storage Addition of text “Bottle containing 5 ml with DROP-TAINER® dispensing system consisting of a transparent low density polyethylene bottle and dispensing plug and white polypropylene closure. Tamper evidence is provided by a security seal around the closure of the bottle. Pack size: box containing 1 bottle.” under Nature and contents of container		
24	Zinforo	Ceftaroline fosamil acetic acid solvate monohydrate	Special warnings and precautions for use	Revision of of text to read "There is no experience with ceftaroline in the treatment of CAP in the following patient groups: the immunocompromised, patients with severe sepsis/septic shock, severe underlying lung disease, (e.g. cystic fibrosis, see section 5.2), those with PORT Risk Class V, and/or CAP requiring ventilation at presentation, CAP due to methicillin-resistant S. aureus or patients requiring intensive care. Caution is advised when treating such patients" under Limitations of the clinical data.	13-Dec-21	Pfizer

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
24	Zinforo	Ceftaroline fosamil acetic acid solvate monohydrate	Preclinical safety data	Revision of text to read "Intravenous bolus dosing of ceftaroline fosamil to suckling rats from post-natal day 7 to 20 was well tolerated at plasma exposures approximately 2-fold higher than those for paediatric patients. Renal cortical cysts were obervedobserved in all groups, including controls, on PND50. The cysts involved a small portion of the kidney and ocurredoccurred in the absence of significant changes in either renal function or urinary parameters. Therefore, these findings were not considered to be adverse" under Juvenile toxicity.	13-Dec-21	Pfizer