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	Azarga	Brinzolamide and timolol maleate	Undesirable effects	Addition of text under psychiatric disorders to include "hallucination"	06-Jul-20	Novartis
2	Cusimolol eye drops	Timolol maleate	Contraindication	Revision of text to read "Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock".	18-Jun-20	Novartis
			Adverse drug reactions	Addition of text under respiratory, thoracic and mediastinal disorders to read "Chronic obstructive pulmonary disease, bronchospasm, cough, wheezing, nasal congestion" as "rare" adverse reactions. Addition of text under general disorders and administration site conditions to include "fatigue" as an "uncommon" adverse effect		
3	Duotrav eye drops	Travoprost and timolol maleate.	Adverse drug reactions	Addition of text under eye disorders to read "Keratitis, iritis, conjunctivitis, anterior chamber inflammation, blepharitis, photophobia, visual acuity reduced, asthenopia, eye swelling, lacrimation increased, erythema of eyelid, growth of eyelashes" as "uncommon" adverse reactions.	18-Jun-20	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Galvus	Vildagliptin	Indication	Revision of text to read "Galvus is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. • as monotherapy. • as combination therapy- • initial combination with metformin when diabetes is not adequately controlled by diet and exercise alone, • in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see section WARNINGS AND PRECAUTIONS, section INTERACTIONS and section CLINICAL STUDIES for available data on different combinations)".	10-Aug-20	Novartis
			Adverse drug reactions	Revision of text in Table 4, from "investigations" to "general disorders and administration site conditions" and and revision of texts under general disorders and administration site conditions from "Weight increase" to "Oedema peripheral" Revision of text in Table 4, from general disorders and administration site conditions" to "investigations" and revision of texts under investigations from "Oedema peripheral" to "Weight increase"		
				Revision of text in Table 6 to read "Metabolism and nutritional disorders: hypoglycaemia " as a common adverse drug reaction" Revision of text in Table 6 to read " Nervous system disorders: Dizziness, tremor" as a common adverse effect.		
				Revision of text to read "Skin and subcutaneous tissue disorders:hyperhidrosis" as a common adverse reac tion Revision of text to read "general disorders and administration site condition: Asthenia" as a common adverse reaction		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Galvus	Vildagliptin	Clinical pharmacology	Revision of text special populations to read " Pediatric patients (below 18 years): No pharmacokinetic data available. Geriatric patients (65 years or above): In otherwise healthy elderly subjects (≥70 years), the overall exposure to vildagliptin (100 mg once daily) was increased by 32% with an 18% increase in peak plasma concentration compared to younger healthy subjects (18 to 40 years). These changes are not considered to be clinically relevant. DPP-4 inhibition by vildagliptin is not affected by age in the age groups studied". Revision of text to include "Ethnicity: There was no evidence that ethnicity affects the pharmacokinetics of vildagliptin". Revision of text to read " Renal impairment: The AUC of vildagliptin increased on average 1.4, 1.7 and 2-fold in patients with mild, moderate and severe renal impairment, respectively, compared to normal healthy subjects. The AUC of the metabolites LAY151 increased 1.6, 3.2 and 7.3-fold and that of BQS867 increased 1.4, 2.7 and 7.3-fold in patients with mild, moderate and severe renal impairment, respectively, compared to healthy volunteers. Limited data from patients with end stage renal disease (ESRD) indicate that vildagliptin exposure is similar to that in patients with severe renal impairment. LAY151 concentrations in ESRD patients were approximately 2 to 3-fold higher than in patients with severe renal impairment. Dosage adjustment may be required in patients with renal impairment. (see section DOSAGE REGIMEN AND ADMINISTRATION). Vildagliptin was removed by hemodialysis to a limited extent (3% over a 3 to 4 hour hemodialysis session starting 4 hours post dose)".	10-Aug-20	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Galvus	Vildagliptin	Clinical studies	Addition of text to include "A five year multi-center, randomized, double blind study (VERIFY) was conducted in patients with type 2 diabetes to evaluate the durability of an early combination therapy with vildagliptin and metformin (N = 998) against standard-of-care initial metformin monotherapy followed by combination with vildagliptin (sequential treatment group) (N = 1003) in newly diagnosed patients with type 2 diabetes. The initiation of an early combination regimen of vildagliptin 50 mg bid plus metformin resulted in a statistically and clinically significant reduction in the relative risk for “time to confirmed initial treatment failure” (HbA1c value ≥ 7%) vs metformin monotherapy in treatment-naïve patients with T2DM over the 5-year study duration. The incidence of initial treatment failure (HbA1c value ≥ 7%) was 429 (43.6%) patients in the combination treatment group and 614 (62.1%) patients in the sequential treatment group (HR [95%CI]: 0.51 [0.45, 0.58]; p<0·001)".	10-Aug-20	Novartis
				Addition of text to include "Consistently lower HbA1c was observed with the combination treatment group compared with the sequential treatment group throughout the study duration. An early combination treatment approach with vildagliptin plus metformin in patients with newly diagnosed type 2 diabetes significantly and consistently improved long-term glycaemic durability compared with sequential treatment. The incidence of adverse events (AE) was comparable between the treatment groups (83.5% in the early combination therapy group vs. 83.2% in the sequential treatment group, respectively). The proportion of newly diagnosed patients who experienced hypoglycemic events over the entire study was low in both treatment groups (1.1% in early combination group and 0.6% in sequential treatment group). Both the treatment groups reported microvascular or macrovascular complications in a comparable proportion of patients (30.5% of patients in the early combination group, and 33.1% of patients in the sequential treatment group). The overall safety and tolerability profile was similar between treatment approaches, with no unexpected safety findings reported".		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Galvus Met	Vildagliptin and Metformin	Indication	Revision of text to read "Galvus Met is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control: • as therapy in patients inadequately controlled with metformin hydrochloride or vildagliptin alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets • as combination therapy- in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycemic control (see sections WARNINGS AND PRECAUTIONS, INTERACTIONS AND CLINICAL STUDIES for available data on different combinations)".	10-Aug-20	Novartis
			Warnings and Precautions	Revision of text under interactions to read "Concomitant medications that may affect renal function, result in significant hemodynamic change or inhibit renal transport and increase metformin systemic exposure should be used with caution (see section INTERACTIONS)".		
			Interactions	Revision of text to read "Drugs that reduce metformin clearance: Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin".		

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5	Galvus Met	Vildagliptin and Metformin	Clinical studies	Addition of text to read "A five year multi-center, randomized, double blind study (VERIFY) was conducted in patients with type 2 diabetes to evaluate the durability of an early combination therapy with vildagliptin and metformin (N = 998) against standard-of-care initial metformin monotherapy followed by combination with vildagliptin (sequential treatment group) (N = 1003) in newly diagnosed patients with type 2 diabetes. The initiation of an early combination regimen of vildagliptin 50 mg bid plus metformin resulted in a statistically and clinically significant reduction in the relative risk for “time to confirmed initial treatment failure” (HbA1c value ≥ 7%) vs metformin monotherapy in treatment-naïve patients with T2DM over the 5-year study duration. The incidence of initial treatment failure (HbA1c value ≥ 7%) was 429 (43.6%) patients in the combination treatment group and 614 (62.1%) patients in the sequential treatment group (HR [95%CI]: 0.51 [0.45, 0.58]; p<0·001)".	10-Aug-20	Novartis
				Addition of text to include "Consistently lower HbA1c was observed with the combination treatment group compared with the sequential treatment group throughout the study duration. An early combination treatment approach with vildagliptin plus metformin in patients with newly diagnosed type 2 diabetes significantly and consistently improved long-term glycaemic durability compared with sequential treatment. The incidence of adverse events (AE) was comparable between the treatment groups (83.5% in the early combination therapy group vs. 83.2% in the sequential treatment group, respectively). The proportion of newly diagnosed patients who experienced hypoglycemic events over the entire study was low in both treatment groups (1.1% in early combination group and 0.6% in sequential treatment group). Both the treatment groups reported microvascular or macrovascular complications in a comparable proportion of patients (30.5% of patients in the early combination group, and 33.1% of patients in the sequential treatment group). The overall safety and tolerability profile was similar between treatment approaches, with no unexpected safety findings reported".		
6	Tasigna	Nilotinib	Adverse drug reaction	Addition of text under Adverse drug reactions from spontaneous reports and literature cases (frequency not known) to include "facial paralysis."	18-Jun-20	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Sirdalud	Tizanidine	Dosage regimen and administration	Addition of text to include "Sirdalud tablet and Sirdalud MR capsule can be taken with or without food (see section CLINICAL PHARMACOLOGY)".	10-Aug-20	Novartis
			Adverse drug reactions	Addition of text to include "Within each system organ class, ADRs are presented in order of decreasing seriousness".		
			Pregnancy, lactation, females and males reproductive potential	Revision of text under contraception-females to read "Sexually-active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1 % pregnancy rates) when using Sirdalud during treatment and for 1 day after stopping treatment with Sirdalud tablet and for 2 days after stopping treatment with Sirdalud MR capsule". Addition of text to read "infertility: There is no data on the effect of Sirdalud on human fertility".		
			Clinical pharmacology	Revision of text under pharmacokinetics (elimination) to include "Tizanidine is eliminated from the systemic circulation with a mean terminal half-life of 2 to 4 hours after Sirdalud tablet administration and 8 to 9 hours after Sirdalud MR capsule administration"		
			Non-clinical safety data	Deletion of text "Reproduction studies performed in rats at a dose of 3 mg/kg/day and in rabbits at 30 mg/kg/day did not show evidence of teratogenicity. Dose levels of 10 and 30 mg/kg/day increased gestation duration in female rats. Prenatal and postnatal pup loss was increased and development retardation occurred. At these doses, dams showed marked signs of muscle relaxation and sedation" under this section.		

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8	Vildagliptin	Vildagliptin	Indication	Revision of text to read "Galvus is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. • as monotherapy. • as combination therapy- • initial combination with metformin when diabetes is not adequately controlled by diet and exercise alone, • in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see section WARNINGS AND PRECAUTIONS, section INTERACTIONS and section CLINICAL STUDIES for available data on different combinations)".	26-Aug-20	Novartis
			Adverse drug reactions	Revision of text in Table 4, from "investigations" to "general disorders and administration site conditions" and and revision of text under general disorders and administration site conditions from "Weight increase" to "Oedema peripheral" Revision of text in Table 4, from general disorders and administration site conditions" to "investigations" and revision of text under investigations from "Oedema peripheral" to "Weight increase" Revision of text in Table 6 to read "Metabolism and nutritional disorders: hypoglycaemia " as a common adverse drug reaction" Revision of text in Table 6 to read " Nervous system disorders: Dizziness, tremor" as a common adverse effect. Revision of text to read "Skin and subcutaneous tissue disorders:hyperhidrosis" as a common adverse reac tion Revision of texts to read "general disorders and administration site condition: Asthenia" as a common adverse reaction		

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9	Voltaren	Diclofenac	Method of Administration	Addition of text under intramuscular in jection to include "and Embolia cutis medicamentosa (Nicolau syndrome))".	18-Jun-20	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
9	Voltaren	Diclofenac	Warnings and precautions	Addition of text to include "Injection site reactions: Injection site reactions have been reported after the administration of Voltaren intramuscularly, including injection site necrosis and embolia cutis medicamentosa, also known as Nicolau Syndrome (particularly after inadvertent subcutaneous administration). Appropriate needle selection and injection technique should be followed during i.m. administration of Voltaren (see section PHARMACEUTICAL INFORMATION - instructions for use and handling)".	18-Jun-20	Novartis
			Adverse drug reaction	Addition of text to include "Adverse drug reactions from post-marketing experience (frequency not known) The following adverse drug reaction has been derived from post-marketing experience with Voltaren. Because this reaction was reported voluntarily from a population of uncertain size, it is not possible to reliably estimate its frequency which is therefore categorized as not known". Addition of table to include" Table 2" and text under Table 2 to include "Injection site reactions: Embolia cutis medicamentosa (Nicolau syndrome)".		
			Instructions for use and handling	Addition of text to include "Appropriate injection technique and length of the needle (considering the thickness of the patient's gluteal fat) should be used to avoid inadvertent subcutaneous administration of Voltaren injection"		