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	Capecitabine	Capecitabine	Posology and method of administration	Modification of text to read "Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Capecitabine tablets should not be crushed or cut." under Method of administration.	26-Jun-20	Sandoz
			Interaction with other medicinal products and other forms of interaction	Modification of text to read " Brivudine: a clinically significant interaction between brivudine and fluoropyrimidines (e.g. capecitabine, 5-Fluorouracil, tegafur), resulting from the inhibition of dihydropyrimidine dehydrogenase by brivudine, has been described. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, brivudine must not be administered concomitantly with capecitabine (see section 4.3 and 4.4). There must be at least a 4-week waiting period between end of treatment with brivudine and start of capecitabine therapy. Treatment with brivudine can be started 24 hours after the last dose of capecitabine" under Interaction with other medicinal products. Modification of text to read "Other than warfarin, no formal interaction studies between capecitabine and other CYP2C9 substrates have been conducted. Care should be exercised when capecitabine is co-administered with 2C9 substrates (e.g., phenytoin). See also interaction with coumarin-derivative anticoagulants below, and section 4.4." under Cytochrome P-450 2C9 substrates.		
			Fertility, pregnancy and lactation	Modification of text to read "Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with capecitabine. If the patient becomes pregnant while receiving capecitabine, the potential hazard to the foetus must be explained. An effective method of contraception should be used during treatment and for 6 months after the last dose of capecitabine. Based on genetic toxicity findings, male patients with female partners of reproductive potential should use effective contraception during treatment and for 3 months following the last dose of capecitabine" under Women of childbearing potential/Contraception in males and females.		
			Pharmacodynamic properties	Addition of text to read "The European Medicines Agency has waived the obligation to conduct studies with capecitabine in all subsets of the paediatric population in adenocarcinoma of the colon and rectum, gastric adenocarcinoma and breast carcinoma (see section 4.2 for information on paediatric use)." under Paediatric population.		

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2	Deslatyne	Desloratadine	Posology and method of administration	Addition of text to read "The safety and efficacy of desloratadine 5 mg film-coated tablets in children below the age of 12 years have not been established. There is limited clinical trial efficacy experience with the use of desloratadine in adolescents 12 through 17 years of age (see sections 4.8 and 5.1)." under Paediatric population for film coated tablets. Modification of text to read "The safety and efficacy of desloratadine 0.5 mg/ml oral solution in children below the age of 1 year have not been established. " under Paediatric population for oral solution.	03-Aug-20	Sandoz
			Special warnings and precautions for use	Modification of text to read "Desloratadine should be administered with caution in patients with medical or familial history of seizures, and mainly young children (See section 4.8), being more susceptible to develop new seizures under desloratadine treatment. Healthcare providers may consider discontinuing desloratadine in patients who experience a seizure while on treatment." under Convulsions.		
			Undesirable effects	Addition of text to read " A retrospective observational safety study indicated an increased incidence of new-onset seizure in patients 0 to 19 years of age when receiving desloratadine compared with periods not receiving desloratadine. Among children 0-4 years old, the adjusted absolute increase was 37.5 (95% Confidence Interval (CI) 10.5 64.5) per 100,000 person years (PY) with a background rate of new onset seizure of 80.3 per 100,000 PY. Among patients 5-19 years of age, the adjusted absolute increase was 11.3 (95% CI 2.3-20.2) per 100,000 PY with a background rate of 36.4 per 100,000 PY. (See section 4.4.)" under this section.		
3	Diamicron	Gliclazide	Special warnings and precautions for use	Addition of text to read " Cases of acute porphyria have been described with some other sulfonylurea drugs, in patients who have porphyria" under Porphyric patients.	20-Jul-20	Les Laboratories Servier
			Undesirable effects	Modification of text to read "Rash, pruritus, urticaria, angioedema, erythema, maculopapular rashes, bullous reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis, and auto-immune bullous disorders), and exceptionally, drug rash with eosinophilia and systemic symptoms (DRESS) disorders" as rarely reported undesireable effects under Skin and subcutaneous tissue disorders.		

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4	Enbrel	Etarnacept	Pharmaceutical form	Deletion of "Pre filled solvent syringes contain 1 mL water for injection. The excipients in Enbrel lyophilized powder are mannitol, sucrose, and trometamol (tromethamine)." under Composition and pharmaceutical characteristics.	23-Jul-20	Pfizer
			Special warnings and precautions for use	Deletion of text "Inflammatory bowel disease (IBD) in patients with juvenile idiopathic arthritis (JIA) There have been reports of IBD in JIA patients being treated with Enbrel, which is not effective for the treatment of IBD. A causal relationship with Enbrel is unclear because clinical manifestations of bowel inflammation have also been observed in untreated JIA patients." under this section.		
			Fertility, pregnancy and lactation	Modification of text to read "The effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. One pregnancy registry compared rates of major birth defects in liveborn infants of mothers with rheumatic diseases or psoriasis exposed to Enbrel in the first trimester (n = 319) versus those unexposed to Enbrel during pregnancy (n = 144). The all inclusive adjusted odds ratio for major birth defects was 2.77 (95% CI 1.04 7.35) and when chromosomal and known genetic disorders were removed was 2.49 (95% CI 0.92 6.68). The findings showed no increased rate of minor malformations, and no pattern of major or minor malformations. In addition, there was no increase in rates of intrauterine or postnatal growth deficits or delayed postnatal development. In a second observational multi country registry study comparing the risk of adverse pregnancy outcomes in women exposed to etanercept (n = 522) to those exposed to non biologic drugs (n = 3508), there was no observed increased risk of major birth defects (adjusted odds ratio 0.96, 95% CI: 0.58 1.60). This study also showed no increased risks of minor birth defects, preterm birth, stillbirth or infections in the first year of life for infants born to women exposed to etanercept during pregnancy. Enbrel should only be used during pregnancy if the potential benefits to the mother outweigh the potential risks to the fetus."		
			Undesirable effects	Addition of "Headache" as an adverse reaction with frequency Very common, under Nervous system disorders in an adverse reaction table. Addition of "Inflammatory bowel disease" as an adverse reaction with frequency Uncommon, under Gastrointestinal disorders in an adverse reaction table. Modification of text to read "Injection site reactions (including bleeding, bruising, erythema, itching, pain, and swelling) and pyrexia" under General disorders and administration site conditions in an adverse reaction table.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Madopar	Levodopa/benserazide hydrochloride	Indications/Uses	Modification of text to read "Madopar is indicated for the treatment of all forms of Parkinson’s syndrome except drug-induced Parkinson’s syndrome. " under this section.	06-Aug-20	Roche
			Dosage/Administration	Addition of text to read "Madopar HBS is indicated for all types of fluctuations in treatment response, in particular those related to plasma concentrations (for example, post-dose dyskinesia or end-of-dose akinesia), and for better control of nocturnal symptoms. Further experience will show whether it is advantageous to use Madopar HBS from the outset in Parkinson patients not previously treated with levodopa alone or in combination with a decarboxylase inhibitor in conventional form." under Parkinson’s disease. Addition of text to read "Patients who experience large fluctuations in the medicine’s effect in the course of the day (“on-off” phenomena) should receive smaller, more frequent single doses. Parkinsonian patients should be informed that their condition may temporarily deteriorate. Patients who experience large fluctuations in response during the day (“on-off” phenomena) should receive smaller, more frequent doses or be switched to sustained-release formulations of Madopar." under Special dosage instructions. Deletion of text to read "Patients who experience large fluctuations in the medicine’s effect in the course of the day (on-off phenomena) should receive more frequent, correspondingly smaller, individual doses, or preferably, the use of Madopar HBS is recommended." under Special dosage instructions. Modification of text to read " The switch to Madopar HBS is preferably made from one day to the next while keeping to the same overall daily dose and dosing frequency. After two to three days, the dosage should be gradually increased by about 50%, because of the lower bioavailability of the active substances in this dosage form. Patients should be informed that their condition may temporarily deteriorate." under Special dosage instructions. Addition of text to read "Excessive responses to treatment (dyskinesia) should be controlled by increasing the interval between doses rather than reducing the single doses. Treatment with standard Madopar or water-soluble Madopar should be resumed if the response to Madopar HBS is inadequate. Patients should be carefully observed for possible undesirable psychiatric symptoms." under Special dosage instructions.		

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5	Madopar	Levodopa/benserazide hydrochloride	Dosage/Administration	Deletion of text to read "Parkinsonian patients should be informed that their condition may temporarily deteriorate. Patients who experience severe fluctuations during the day (on-off phenomena) should take smaller and more frequent doses. Patients should be carefully monitored for possible psychiatric side effects." under Special dosage instructions.	06-Aug-20	Roche
			Warnings and precautions	Modification of text to read "Dopaminergic dysregulation syndrome (DDS): Dopamine dysregulation syndrome (DDS) has been observed in some patients treated with Madopar and is an addictive disorder that leads to excessive use of this or other dopaminergic drugs. Before initiation of treatment, patients and caregivers must be warned of the potential risk of developing DDS (see Undesirable effects)." under Potential for drug dependence or abuse.		
			Interactions	Modification of text to read "Coadministration of the anticholinergic agent trihexyphenidyl with non-prolonged-release Madopar reduces the rate, but not the extent, of levodopa absorption. However, coadministration of trihexyphenidyl with Madopar HBS does not affect the pharmacokinetics of levodopa." Modification of text to read "Antihypertensives, neuroleptics, opioids-Because of a possible additive effect, the patient's blood pressure must be regularly monitored when Madopar is given in conjunction with antihypertensive agents. Neuroleptics, opioids and reserpine-containing antihypertensive medications antagonise the action of Madopar." under Pharmacodynamic interactions.		

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5	Madopar	Levodopa/benserazide hydrochloride	Undesireable effects	Revision of text to read "There have been rare reports of hemolytic anemia, moderate and transient leukopenia and thrombocytopenia, and a reduced thromboplastin time. Rises in blood urea nitrogen (BUN) have been observed with Madopar. Therefore, as in any long-term treatment with drugs containing levodopa, the blood count should be checked periodically together with hepatic and renal function." under Blood and lymphatic system disorders. Addition of text to read "Frequency not known: dopamine dysregulation syndrome. Dopamine dysregulation syndrome (DDS) is an addictive disorder observed in some patients treated with Madopar. Affected patients show compulsive misuse of dopaminergic drugs, taking higher doses than needed for adequate control of motor symptoms of Parkinson's disease. In some cases this may lead to severe dyskinesia (see Warnings and precautions)." under Psychiatric disorders. Addition of text "Uncommon: headache." under Nervous system disorders. Addition of text to read " Reporting of suspected adverse reactions after marketing authorisation is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product." under Investigations. Addition of text "Not reported" under Clinical efficacy.	06-Aug-20	Roche
			Pharmacokinetics	Addition of text to read " Controlled-release form-The pharmacokinetic properties of Madopar HBS differ from those of the conventional capsules and tablets and the water-soluble tablets. The active ingredients are released slowly in the stomach. Maximum plasma concentrations, which are 20-30% of those achieved with the standard dosage forms, are reached about 3 hours after administration of Madopar HBS. The plasma concentration-time curve shows a longer "half-value duration" (time span until plasma levels return to half the maximum concentration) than with the conventional forms, which indicates pronounced controlled-release properties. The bioavailability of HBS capsules is 50-70% of that of standard Madopar and is not affected by food. Maximum plasma concentrations of levodopa are not affected by food when Madopar HBS is taken after meals, but occur later (by some 5 hours)." under Absorption.		
			Other information	Revision of text to read " Do not use this medicine after the expiry date ("EXP") stated on the pack. Madopar Dispersible should be drunk within half an hour of its dissolution." under Shelf-life.		

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6	Topamax	Topiramate	What you need to know before you take Topamax	Addition of text to read "This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'." under Other ingredients.	30-Jun-20	Janssen
			Possible side effects	Addition of " Inflammation of the eye (uveitis) with symptoms such as eye redness, pain, sensitivity to light, runny eyes, seeing small dots or getting blurred vision." as an adverse reaction with frequency "Not known (cannot be estimated from the available data)" under this section.		