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	Benylin four flu liquid	Diphenhydramine hydrochloride, Pseudoephedrine hydrochloride and paracetamol	Posology and method of administration	Addition of text under sub-section Hepatic dysfunction to read "BENYLIN FOUR FLU LIQUID is contraindicated in patients with severe hepatic impairment (see section 4.3)." Addition of text under sub-section Renal dysfunction to read "BENYLIN FOUR FLU LIQUID should not be used by patients with renal impairment (see section 4.3)."	03/10/2024	Johnson & Johnson (Pty) Ltd
			Contraindications	Addition of text to read "• Severe acute or chronic kidney disease/renal failure. • Prostate disease. • Patients with difficulty in urination. • Concomitant administration with sympathomimetics, beta-blockers and other pseudoephedrine-, paracetamol- or diphenhydramine-containing medicines. • Diabetes mellitus and severe renal impairment."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	Benylin four flu liquid	Diphenhydramine hydrochloride, Pseudoephedrine hydrochloride and paracetamol	Special warnings and precautions for use	Revision of text to include "Cases of Posterior Reversible Encephalopathy Syndrome (PRES) and Reversible Cerebral Vasoconstriction Syndrome (RCVS) have been reported with the use of pseudoephedrine-containing products (see section 4.8). The risk is increased in patients with severe or uncontrolled hypertension, or with severe acute or chronic kidney disease/renal failure (see section 4.3). Pseudoephedrine should be discontinued and immediate medical assistance sought if the following symptoms occur: sudden severe headache or thunderclap headache, nausea, vomiting, confusion, seizures and/or visual disturbances. Most reported cases of PRES and RCVS resolved following discontinuation and appropriate treatment. Large doses may precipitate fits in epileptics. Deepening coma, extrapyramidal effects and photosensitisation of the skin may occur. The positive results of skin tests may be suppressed." Revision of text to read "Dosages in excess of those recommended (overdose) may cause severe liver or kidney damage (see section 4.9). In case of overdose, get medical help immediately. Quick medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms."	03/10/2024	Johnson & Johnson (Pty) Ltd

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	Benylin four flu liquid	Diphenhydramine hydrochloride, Pseudoephedrine hydrochloride and paracetamol	Special warnings and precautions for use	Revision of text to read "Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCARs, treatment with BENYLIN FOUR FLU LIQUID must immediately be discontinued and appropriate treatment instituted."	03/10/20245	Johnson & Johnson (Pty) Ltd
			Interaction with other medicines and other forms of interaction	Revision of text to read "Caution should be taken when paracetamol, as contained in BENYLIN® FOUR FLU LIQUID, is used concomitantly with flucloxacillin, as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors (see section 4.4)."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	Benylin four flu liquid	Diphenhydramine hydrochloride, Pseudoephedrine hydrochloride and paracetamol	Fertility, pregnancy and lactation	Addition of text under sub-section Diphenhydramine to read "Diphenhydramine, as contained in BENYLIN FOUR FLU LIQUID, crosses the placenta and is excreted into breast milk, but levels have not been reported."	03/10/2024	Johnson & Johnson (Pty) Ltd

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
1	Benylin four flu liquid	Diphenhydramine hydrochloride, Pseudoephedrine hydrochloride and paracetamol	Fertility, pregnancy and lactation	Addition of text under sub-section Paracetamol to read "A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency." Addition of text to read uder sub-section Pseudoephedrine "Pseudoephedrine distributes into and is concentrated in breast milk. Up to 0,7 % of a single 60 mg dose of pseudoephedrine may be distributed into breast milk over 24 hours. Pseudoephedrine concentrations in milk are from 2 to 3-fold higher than those in plasma. This milk/plasma medicine concentration profile suggests low protein binding, although no protein plasma binding data in humans are available. Data from a study of lactating mothers taking 60 mg pseudoephedrine every 6 hours suggests that from 2,2 to 6,7 % of the maximum daily dose (240 mg) may be available to the infant from a breastfeeding mother."	03/10/2024	Johnson & Johnson (Pty) Ltd

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Carbetocin ferring	Carbetocin	Special warnings and precautions for use	Addition of sub-heading "Water retention" Revision of text under sub section water retention to read "Animal studies have shown carbetocin to possess some antidiuretic activity (vasopressin activity: <0.025 I.U./vial) and therefore the risk of water intoxication with hyponatraemia cannot be excluded, especially in patients receiving large volumes of infusion solutions. Attention should be paid to the early signs of water intoxication or hyponatraemia - such as drowsiness, listlessness and headache - to prevent complications such as convulsions and coma." Addition of sub-heading "Cardiac risks (including QT-prolongation)"	11/11/2024	Ferring Pharmacueticals

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Carbetocin ferring	Carbetocin	Special warnings and precautions for use	Revision of text under sub-section Cardiac risks (including QT-prolongation) to read "Cardiac undesirable effects such as bradycardia, QT-prolongation, arrhythmias and myocardial ischaemia have been observed, especially following on rapid intravenous injection of oxytocin in doses of several I.U. as bolus. It is not known whether these changes are causally related to the oxytocin treatment, or were caused by simultaneously administered co-medication. There are no data on a possible pathophysiological mechanism. The occurrence of such undesirable effects also under carbetocin cannot be excluded, since carbetocin is structurally closely related to oxytocin. Therefore, carbetocin should only be used with special caution in patients with known long-QT syndrome or other risk factors for QT prolongation (such as co-medication with drugs with a known risk of QT-prolongation)." Addition of sub-heading to include "Further precautions"	11/11/2024	Ferring Pharmacueticals

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Carbetocin ferring	Carbetocin	Pregnancy and lactation	Addition of text under sub-section breastfeeding "Breast-feeding can be started without restrictions after the use of carbetocin."	11/11/2024	Ferring Pharmacueticals
3	Intelence	Etravirine	Special warnings and precautions for use	Deletion of text to read "While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines."	10/03/2024	Janssen
			Fertility, pregnancy and lactation	Revision of text under sub-section breastfeeding "Because of the potential for adverse events in nursing infants, women should be instructed not to breastfeed if they are receiving INTELENCE. It is recommended that women infected living with HIV do not breastfeed in order to avoid transmission of HIV."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Jardiance	Empagliflozin	Special population	Revision of text to include ''The recommended starting dose is 10 mg empagliflozin once daily. In patients tolerating empagliflozin 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily (see sections 5.1 and 5.2). No data are available for children with eGFR <60ml/min/1.73 m² and children below 10 years of age. The safety and efficacy of empagliflozin for the treatment of heart failure or for the treatment of chronic kidney disease in children under 18 years of age have not been established. No data are available.'' Under sub-section Paediatric population	11/11/2024	Boehringer Ingelheim
			Method of administration	Addition of text under 4.4 Special warnings and precautions for use to include ''Empagliflozin should not be used in patients with type 1 diabetes mellitus (see “ketoacidosis” in section 4.4).'' Under sub-section General.		
			4.5 Interaction with other medicinal products and other forms of interaction	Addition of text under sub-section Paediatric population to include ''Interaction studies have only been performed in adults.''		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Jardiance	Empagliflozin	4.8 Undesriable effects	Addition of text to include ''n the DINAMO trial 157 children aged 10 years and above with type 2 diabetes were treated, in which 52 patients received empagliflozin, 52 linagliptin and 53 placebo (see section 5.1). During the placebo-controlled phase, the most frequent adverse drug reaction was hypoglycaemia with higher overall rates for patients in the empagliflozin pooled group compared with placebo (empagliflozin 10 mg and 25 mg, pooled: 23.1%, placebo: 9.4%). None of these events was severe or required assistance. Overall, the safety profile in children was similar to the safety profile in adults with type 2 diabetes mellitus.	11/11/2024	Boehringer Ingelheim

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Jardiance	Empagliflozin	4.8 Undesriable effects	Addition of text under Type 2 diabetes mellitus ''The clinical efficacy and safety of empagliflozin (10 mg with a possible dose-increase to 25 mg) and linagliptin (5 mg) once daily has been studied in children and adolescents from 10 to 17 years of age with type 2 diabetes mellitus in a placebo-controlled study (DINAMO) over 26 weeks, with a safety extension period up to 52 weeks. Background therapies as adjunct to diet and exercise included metformin (51%), a combination of metformin and insulin (40.1%), insulin (3.2%), or none (5.7%). The adjusted mean change in HbA1c at week 26 between empagliflozin (N=52) and placebo (N=53) of -0.84% was clinically meaningful and statistically significant (95CI -1.50, -0.19; p=0.0116). In addition, treatment with empagliflozin versus placebo resulted in a clinically meaningful adjusted mean change in FPG of -35.2 mg/dl (95% CI -58.6, -11.7) [-1.95 mmol/l (-3.25, -0.65)].''	11/11/2024	Boehringer Ingelheim
5	Meronem	Meropenem Trihydrate	Undesirable effects	Addition of text under tabulated risk of adverse reactions Table 1: System organ class "Psychiatric disorders" with frequency "rare" and event "delirium".	28/10/2024	Pfizer

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	Medrol	Methylprednisolone	Special warnings and precautions for use	Revision of text to read "Corticosteroids may increase susceptibility to infection, may mask some signs of infection, exacerbate existing infections, increase the risk of reactivation or exacerbation of latent infections and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections with any pathogen, including viral, bacterial, fungal, protozoan or helminthic organisms, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Monitor for the development of infection and consider withdrawal of corticosteroids or dosage reduction as needed. " Under sub secton Immunosuppressant Effects/Increased Susceptibility to Infections	05/11/2024	Pfizer

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	Medrol	Methylprednisolone	4.5. Interactions with other medicinal products and other forms of interaction	Addtion of text in table 1 under Drug Class or Type DRUG or SUBSTANCE to reafd "Anticoagulants (oral) -VITAMIN K ANTAGONISTS" with Interaction/Effect "The effect of methylprednisolone on vitamin K antagonists (e.g., warfarin, acenocoumarol, fluindione) is variable. There are reports of enhanced as well as diminished effects of these anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.	05/11/2024	Pfizer
7	Synjardy	Empagliflozin and metformin hydrochloride	What you need to know before you take Synjardy	Revision of text to read ''if you experience rapid weight loss, feeling sick or being sick, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, contact a doctor or the nearest hospital straight away and stop taking this medicine until further advice from your doctor.''	11/11/2024	Boehringer Ingelheim

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Synjardy	Empagliflozin and metformin hydrochloride	How to take Synjardy	Addition of text to read ''Do not stop taking Synjardy without first consulting your doctor, unless you suspect you have diabetic ketoacidosis, lactic acidosis, or if you have a condition that may be associated with dehydration (see section 2 “warnings and precautions”).	11/11/2024	Boehringer Ingelheim

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
8	Ziinacef	Cefuroxime sodium	Warnings and precautions for use	Addition of text to include under sub- section Hypersensitivity reactions to read " There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8). Revision of text under sub-section Severe cutaneous adverse reactions (SCARS) to read “Severe cutaneous adverse reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with cefuroxime treatment (see section 4.8). At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, cefuroxime should be withdrawn immediately and an alternative treatment considered. If the patient has developed a serious reaction su cefuroxime must not be restarted in this patient at any time.)	28/10/2024	Sandoz