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	Undesirable effect	Addition of text under rare adverse effects to include "Angioedema (the swelling of the deeper layers of the skin, caused by a build-up of fluid)".	06-May-21	Sandoz Pharmaceuticals d.d.
2	Ceftriazone sandoz	Ceftriazone Sodium	Warnings and precautions	Addition of text under "talk to your doctor or pharmacist or nurse before you are given Ceftriazone Sandoz if" to include "You are elderly and have been diagnosed with severe renal impairment or a central nervous system disorder"	07-May-21	Sandoz Pharmaceuticals d.d.
			Undesirable effect	Addition of texts under rare adverse effects to include "Changes in consciousness levels and mental state in particularly in older patients with severe renal impairment"		
3	CellCept	Mycophenolate mofetil	Warnings and precautions	Revision of text to read "Due to the cytostatic effect of CellCept on B and T lymphocytes, COVID-19 may follow a more severe course. Dose reduction or discontinuation of CellCept should be considered in patients with evidence of BK virus-associated nephropathy or in cases of clinically significant COVID-19".	29-Apr-21	Roche Products Ghana Ltd
			Undesirable effect	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. Healthcare professionals are asked to report any suspected new or serious adverse".		
4	Dalacin C	Clindamycin	Therapeutic indication	Revision of text to read "Pneumocystis jirovecii (previously classified as Pneumocystis carinii) pneumonia in patients with AIDS. In patients who are intolerant to, or do not respond adequately to conventional treatment, clindamycin may be used in combination with primaquine."	05-Aug-21	Pfizer
				Revision of text to read " Clindamycin phosphate, when used concurrently with an aminoglycoside antibiotic such as gentamicin or tobramycin, has been shown to be effective in preventing peritonitis or intra-abdominal abscess after bowel perforation and bacterial contamination secondary to trauma.		

4	Dalacin C	Clindamycin	Special warnings and precautions for use	Revision of text to read "Pseudomembraneous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider the diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents."	05-Aug-21	Pfizer
				Revision of text to read "If therapy is prolonged, liver function tests should be performed. Clindamycin 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 effect	Addition of text under renal and urinary disorders to include "acute kidney injury"		
			Pharmacological Properties	Addition of text under Pharmacokinetic properties to read "Obese Pediatric Patients Aged 2 to Less than 18 Years and Obese Adults Aged 18 to 20 Years: An analysis of pharmacokinetic data in obese pediatric patients aged 2 to less than 18 years and obese adults aged 18 to 20 years demonstrated that clindamycin clearance and volume of distribution normalized by total body weight are comparable regardless of obesity."		
5	Durogesic	Fentanyl patch	Warnings and precautions	Addition of text to read "Store this medicine in a safe and secure place, where other people cannot access it - see section 5 for more information."	16-Aug-21	Janssen Pharmacutical Companies of Johnson & Johnson
			Special precautions for use	Addition of text to include "Talk to your doctor or pharmacist before using this medicine if any of the following apply to you: You are a smoker, You have ever had problems with your mood (depression, anxiety or a personality disorder) or have been treated by a psychiatrist for other mental illness.Addition of texts to read "Store this medicine in a safe and secure place, where other people cannot access it - see section 5 for more information."		

5	Durogesic	Fentanyl patch	Special precautions for use	Addition of text to include "While using the patch, tell your doctor if you have breathing problems while sleeping. Opioids like DUROGESIC can cause sleep-related breathing disorders such as breathing pauses during sleep (sleep apnoea) and low oxygen level in the blood (sleep-related hypoxaemia). Tell your doctor if you, your partner or carer notice you have any of the following: breathing pauses during sleep, night awakening due to shortness of breath, difficulties staying asleep, you feel excessively drowsy during the day. Your doctor may decide to change your dose. While using the patch, tell your doctor if you notice a change in the pain you are feeling. If you feel: your pain is no longer relieved by the patch, an increase in pain, there is a change in how you feel the pain (for example, you feel pain in another part of your body), pain when something touches your body that you wouldn't expect to hurt you. Do not change the dose yourself. Your doctor may decide to change your dose or treatment."	16-Aug-21	Janssen Pharmacutical Companies of Johnson & Johnson
			Undesirable effects	Revision of text to read " Repeated, long -term use of the patches may make the medicine less effective (you get used to it, or you may become more sensitive to pain), or you may become dependent on it. Increasing the dose of your patches may help to further reduce your pain for a while, but it may also be harmful. If you notice that your medicine is working less properly, talk to your doctor. Your doctor will decide whether it is better for you to increase the dose or to gradually decrease your use of this medicine. Also if you have concern that you may become addicted (dependent), you can consult your doctor on this. See Read section 4 for a full list of possible side effects."		
				Addition of text to read "Withdrawal symptoms when stopping DUROGESIC: Do not suddenly stop taking this medicine. Withdrawal symptoms such as restlessness, difficulty sleeping, irritability, agitation, anxiety, feeling your heartbeat (palpitations), increased blood pressure, feeling or being sick, diarrhoea, you have less appetite for food, shaking, shivering or sweating may occur. If you want to stop taking this medicine, talk to your doctor first. Your doctor will tell you how to do this. Usually this is done by reducing the dose gradually, so that you will suffer less from any unpleasant withdrawal effects."		

5	Durogesic	Fentanyl patch	Interaction with other medicinal products and other forms of interaction	Revision of text to read "The risk of side effects increases if you are taking medicines such as certain antidepressants. DUROGESIC may interact with these medicines and you may experience changes to mental status such as feeling agitated, seeing, feeling, hearing, or smelling things that are not there (hallucinations) and other effects such as changing blood pressure, fast heart beat, high body temperature, overactive reflexes, lack of coordination, muscle stiffness, nausea, vomitting and diarrhoea (these could be signs of Serotonin Syndrome). If used together, your doctor may want to closely monitor you for such side effects in particular when starting treatment or when the dose of your medicine is changed."	16-Aug-21	Janssen Pharmacutical Companies of Johnson & Johnson
				Revision of text under Use with central nervous system depressants, including alcohol and some narcotic drugsto read "Concomitant use of DUROGESIC and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, you can only use DUROGESIC together with other medicines when other treatment options are not possible. However if your doctor does prescribe DUROGESIC together with sedative medicines, your doctor should keep the dose as low as possible and the duration should be as short as possible. Please tell your doctor about all sedative medicines you are taking, and follow your doctor’s dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.		
			Pregnancy and breastfeeding	Addition of text to read "Prolonged use of DUROGESIC during pregnancy can cause withdrawal symptoms (such as highpitched cry, jitteriness, fits, poor feeding and diarrhoea) in your newborn baby. These withdrawal symptoms can be life-threatening if not recognised and treated. Talk to your doctor immediately if you think your baby may have withdrawal symptoms."		

5	Durogesic	Fentanyl patch	Dosage and method of administration	Revision of text under if you want to stop using the patches to read "Do not suddenly stop taking this medicine. If you want to stop taking this medicine, talk to your doctor first. Your doctor will tell you how to do this. Usually this is done by reducing the dose gradually, so that you will suffer less from any unpleasant withdrawal effects. See also section 2 'Withdrawal symptoms when stopping DUROGESIC'."	16-Aug-21	Janssen Pharmacutical Companies of Johnson & Johnson
			Other Information	Addition of text under where you should keep the patches to include "Store this medicine in a safe and secure place, where other people cannot access it. It can cause serious harm and be fatal to people who may take this medicine by accident, or intentionally when it has not been prescribed for them."		
6	Flarex	Fluorometholone acetate	Name of Medicinal Product	Addition of text to read "FLUCON® 0.1% eye drops, suspension".	28-Jul-21	Novartis International AG
			Qualitative and Quantitative Composition	Addition of text to read "Active ingredient for Flucon is 1.0 mg fluorometholone in one mL suspension (0.1%)".		
				Addition of text under excipient to read "Flucon: Polyvinyl alcohol, sodium chloride, disodium phosphate anhydrous, hypromellose, polysorbate 80, sodium dihydrogen phosphate monohydrate, disodium edetate, benzalkonium chloride, hydrochloric acid, sodium hydroxide, purified water. Information might differ in some countries".		
			Posology and method of administration	Addition of text to include "Geriatric patients (65 years of age or above): No dosage regimen adjustment is required in patients 65 years of age or above".		
				Addition of text under method of administration to read "Eye drops are not for injection. They should never be injected subconjunctivally, nor should they be directly introduced into the anterior chamber of the eye".		
				Addition of text to include " It is advisable that the intraocular pressure be routinely monitored".		
			Fertility, pregnancy and lactation	Addition of subheading under pregnancy to include "Animal data"		

6	Flarex	Fluorometholone acetate	Fertility, pregnancy and lactation	Revision of text under animal data to read "An embryo-fetal development study was conducted in rabbits. Fluorometholone was ocularly instilled to both eyes at doses of 0.075, 0.15, 0.30 and 0.60 mg/day from gestation day 6 to 18, targeting the period of organogenesis. Maternal body weight gain increased during the first 4 days of treatment followed by a decrease until the end of the treatment at all dose levels. Dose related increase in the incidence of total litter losses (abortion and/or total resorption), higher fetal loss, lower litter size and lower litter and mean pup weights were noted. An increased incidence of minor anomalies and major malformations including cleft palate, deformed rib cage, anomalous limbs, encephalocele, craniorachischisis, and spina bifida occurred at all doses. The lowest dose (0.075 mg/rabbit) in this study corresponds to a dose ratio of about 0.1 (based on body surface area), when compared to the maximum recommended human ocular dose of 0.048 mg/kg/day".	28-Jul-21	Novartis International AG
			Clinical Pharmacology	Adddition of text under pharmacokinetics of Flucon to read "Absorption and distribution: Following topical ocular administration of 0.1% fluorometholone in 22 adult patients undergoing cataract surgery, the maximum fluorometholone concentration of 5.1 ng/mL in aqueous humor was observed at 0.5-1 hour post dose. Biotransfoemation/Metabolism: Fluorometholone is metabolized in humans by reduction of the 6,7 alkane bond to form 6,7- dehydro-fluorometholone as well as hydroxylation to form 6-hydroxy-fluorometholone. These two metabolites undergo further oxidation to form 6,7-dehydro-20-hydroxy-fluorometholone and 6,20 dehydroxy-fluorometholone, respectively".		
				Addition of text under pharmacokinetics for Flarex to read "Biotransformation/metabolism Fluorometholone acetate is an ester which is subject to rapid hydrolysis in ocular tissues as well as blood. The principal metabolite is fluorometholone which is likely to undergo further systemic metabolism as described above".		
				Addition of text under pharmacokinetics for Flarex and Flucon to read "Elimination: The elimination pathway of topical ocular administered fluorometholone and its metabolites had not been reported. Most topical corticosteroids are metabolized in the liver and their metabolites excreted in urine and bile".		

6	Flarex	Fluorometholone acetate	Clinical Pharmacology	Addition of text under pharmacokinetic for Flarex and Flucon to read "Linearity/non-linearity: Ocular uptake studies evaluating dose-proportionality of either fluorometholone or fluorometholone acetate have not been conducted".	28-Jul-21	Novartis International AG
				Addition of text under pharmacokinetic for Flarex and Flucon to read "PK/PD relationship: A specific PK/PD model has not been established for fluorometholone. Corticosteroids cause a rise in intraocular pressure in susceptible individuals. In a small study, Flarex eye drops, suspension and Flucon eye drops, suspension demonstrated a significantly longer average time to produce a rise in intraocular pressure than did dexamethasone phosphate; however, the ultimate magnitude of the rise was equivalent for both drugs and in a small percentage of individuals a significant rise in intraocular pressure occurred within 1 week. Published literature reports fluorometholone has a dose-dependent ocular hypertensive effect, particularly in steroid responders and children, although less-pronounced compared to dexamethasone".		
				Addition of subheading under pharmacokinetic for Flarex and Flucon to read " Special population"		
				Addition of text under special population to read "Hepatic Impairment, Renal Impairment and Geriatric Patients: Studies evaluating the pharmacokinetics with Flarex or Flucon eye drop suspensions in patients with hepatic and renal impairment or in geriatric patients have not been conducted		

6	Flarex	Fluorometholone acetate	Clinical Pharmacology	Addition of text under special population to read "Pediatric use (See sections 4 Dosage regimen and administration and 6 Warnings and precautions): When fluorometholone is used in children, a lower frequency and shorter duration of usage is recommended. The ocularhypertensive response in children occurs more frequently, more severely, and more rapidly than that reported in adults. Additionally, ocular corticosteroids including fluorometholone are associated with systemic activity which can cause temporary growth suppression in children. Flarex and Flucon are not indicated in children under 3 years old. No specific studies have been conducted in this age group. Use of fluorometholone in children under the age of 3 is limited to a single published study (n=21). Transient ocular hypertension induced by fluorometholone could not be observed, however there were no sustained or long-term effects on optic nerve health, and a normal course of ocular growth was observed in these children"	28-Jul-21	Novartis International AG
			Special precautions for storage	Addition of text to read "Flucon: Do not store above 25°C. Information might differ in some countries".		
7	Lodoz	Bisoprolol/hydrochlorthiazide	Special warnings and precautions for use	Addition of subheading to read "Choroidal effusion, acute myopia and secondary angle-closure glaucoma" Revision of texts under Choroidal effusion, acute myopia and secondary angle-closure glaucoma to read "Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma"	07-Sep-21	Merck
			Undesirable effects	Addition of text to include "choroidal effusion" under eye disorders.		
8	Ocrevus	Ocrelizumab	Warnings and precautions	Addition of text to include "Late neutropenia- Cases of late-onset neutropenia have been reported. Although some cases were grade 3 or 4, the majority of the cases were grade 1 or 2. Cases of late-onset neutropenia have been reported at least 4 weeks after the last Ocrevus infusion. In patients with signs and symptoms of infection, measurement of blood neutrophils is recommended (see “Undesirable effects”)."	19-Aug-21	Roche Products Ghana Ltd
			Undesirable effects	Addition of text to read "Not known (cannot be estimated from the available data): Late-onset neutropenia*. * Observed in the post-marketing setting.		

9	Ovitrelle	Choriogonadotropin alfa	Contraindications	Deletion of text that read "Extrauterine pregnancy in the previous 3 months"	07-Sep-21	Merck
				Revision of text to read "Ovitrelle must not be used in conditions when an effective response cannot be obtained, such as primary ovarian failure, malformations of sexual organs incompatible with pregnancy, fibroid tumours of the uterus incompatible with pregnancy, postmenopausal women"		
			Special warnings and precautions for use	Addition of text to read "Traceability: In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded." Addition of subheading to read "General recommendations"		
				Revision of text under Ovarian hyperstimulation syndrome (OHSS) to read "A certain degree of ovarian enlargement is an expected effect of controlled ovarian stimulation. It is more commonly seen in women with polycystic ovarian syndrome and usually regresses without treatment. In distinction to uncomplicated ovarian enlargement, OHSS is a condition that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities. Mild manifestations of OHSS may include abdominal pain, abdominal discomfort and distension, and enlarged ovaries. Moderate OHSS may additionally present with nausea, vomiting, ultrasound evidence of ascites and marked ovarian enlargement. Severe OHSS further includes symptoms such as severe ovarian enlargement, weight gain, dyspnoea or oliguria. Clinical evaluation may reveal signs such as hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, pleural effusions, or acute pulmonary distress. Very rarely, severe OHSS may be complicated by ovarian torsion or thromboembolic events, such as pulmonary embolism, ischaemic stroke or myocardial infarction."		

9	Ovitrelle	Choriogonadotropin alfa	Special warnings and precautions for use	Revision of text under Ovarian hyperstimulation syndrome (OHSS) to read "Independent risk factors for developing OHSS include young age, lean body mass, polycystic ovarian syndrome, higher doses of exogenous gonadotropins, high absolute or rapidly rising serum estradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in ART cycles. Adherence to recommended Ovitrelle dosage and regimen of administration can minimise the risk of ovarian hyperstimulation. Monitoring of stimulation cycles by ultrasound scans as well as estradiol measurements are recommended to early identify risk factors. There is evidence to suggest that hCG plays a key role in triggering OHSS and that the syndrome may be more severe and more protracted if pregnancy occurs. Therefore, if signs of ovarian hyperstimulation occur, it is recommended that hCG be withheld and the patient be advised to refrain from coitus or use barrier contraceptive methods for at least 4 days. As OHSS may progress rapidly (within 24 hours) or over several days to become a serious medical event, patients should be followed for at least two weeks after hCG administration. Mild or moderate OHSS usually resolves spontaneously. If severe OHSS occurs, it is recommended that gonadotropin treatment be stopped and that the patient be hospitalised and appropriate therapy be started.	07-Sep-21	Merck
				Revision of text under multiple pregrancy to read "In patients undergoing induction of ovulation, the incidence of multiple pregnancy and births is increased compared with natural conception. The majority of multiple conceptions are twins. Multiple pregnancies, especially high order, carry an increased risk of adverse maternal and perinatal outcomes. To minimise the risk of higher order multiple pregnancy, careful monitoring of ovarian response is recommended. ART procedures the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the patient age.		
				Revision of text to read "Pregnancy loss: The incidence of pregnancy loss by miscarriage or abortion is higher in patients undergoing stimulation of follicular growth for ovulation induction or ART than following natural conception."		

9	Ovitrelle	Choriogonadotropin alfa	Special warnings and precautions for use	Revision of text under ectopic pregnancy to read "Women with a history of tubal disease are at increased risk for ectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatments. The prevalence of ectopic pregnancy after ART in this population was reported to be higher than in the general population."	07-Sep-21	Merck
				Addition of text to include "Reproductive system neoplasms: There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple treatment regimens for infertility. It is not yet established whether or not treatment with gonadotropins increases the risk of these tumours in infertile women.		
			Fertility, pregnancy and lactation	Addition of text to read "Data on a limited number of exposed pregnancies indicate no increased risks of malformation or foeto/neonatal toxicity"		
			Undesirable effects	Deletion of text that read "Psychiatric disorders: Uncommon: Depression, irritability, restlessness"		
				Addition of text under gastrointestinal disorders to read " Abdominal distension"		
				Deletion of text that read "Skin and subcutaneous tissue disorders: Very rare: Mild reversible skin reactions manifesting as rash"		
				Deletion of text that read "Ectopic pregnancy, ovarian torsion and other complications have been reported in patients after hCG administration. These are considered concomitant effects related to assisted reproductive techniques."		
				Deletion of text under Reproductive system and breast disorders that read "breast pain"		
				Deletion of text under General disorders and administration site conditions that read "tiredness"		
10	Pegasys	Peginterferon alfa-2a	Composition	Revision of text under active ingredient to read "Peginterferon alfa-2a (recombinant interferon alfa-2a conjugated to bis-[monomethoxy polyethylene glycol]. Produced by genetic engineering using E. coli cells)."	19-Aug-21	Roche Products Ghana Ltd

10	Pegasys	Peginterferon alfa-2a	Composition	Revision of text under excipient to read "Each vial contains Polysorbate 80 (produced from genetically modified maize); sodium acetate trihydrate; sodium chloride (corresponding to a total of 3.6 mg sodium per 1 ml vial); glacial acetic acid, benzyl alcohol (E1519 10.0 mg per 1 ml vial, water for injection. Each prefilled syringe contains Polysorbate 80 (produced from genetically modified maize); sodium acetate trihydrate; sodium chloride (corresponding to a total of 1.8 mg sodium per 0.5 ml prefilled syringe);glacial acetic acid; benzyl alcohol (E1519) 5.0 mg per prefilled syringe, water for injection."	19-Aug-21	Roche Products Ghana Ltd
			Therapeutic indication	Revision of text under treatment of chronic hepatitis C (CHC) in adult patients t read "Pegasys in combination with ribavirin: The combination of Pegasys and ribavirin is indicated in treatment-naïve patients and patients who have not responded to previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin. Efficacy has also been established in HCV patients with clinically stable HIV coinfection. In previously treated patients the interval between the end of the previous treatment and the restarted treatment in the main study was at least 12 weeks and on average more than one year (see Properties/Effects). Patients must not have decompensated liver disease, and chronic hepatitis C must be confirmed by serum markers (anti-HCV antibodies, HCV RNA). Histological confirmation of the diagnosis should normally be obtained. When Pegasys is used in combination with ribavirin, the prescribing information on ribavirin should also be consulted. Pegasys as monotherapy: Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin. Monotherapy has not been tested in patients with normal transaminases."		
			Dosage and method of administration	Addition of text to include "Interferons can cause unusual tiredness. If self-injected by the patient, the product should be administered at bedtime." Addition of text to read "To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment."		

10	Pegasys	Peginterferon alfa-2a	Dosage and method of administration	Deletion of text under Chronic hepatitis C that read "The dose of ribavirin for use in combination with Pegasys depends on viral genotype: for genotype 2 or 3 the dose is 800 mg p.o./day, for genotype 1 it is 1000–1200 mg p.o./day, depending on body weight (see Table 1)." Deletion of text that read "Ribavirin should be taken with meals." Deletion of text under general that read "As such dose reductions to 90 or 45 g cannot be administered using the prefilled pen, the reduced dose must be administered using the prefilled syringe."	19-Aug-21	Roche Products Ghana Ltd
				Addition of text under special dosage instructons to read "Patients with hepatic impairment: In patients with compensated cirrhosis (e.g. Child-Pugh A), Pegasys has been shown to be effective and safe. Pegasys has not been evaluated in patients with decompensated cirrhosis (e.g. Child-Pugh B or C or bleeding oesophageal varices) (see “Contraindications”). The Child-Pugh classification divides patients into groups A, B and C, or “Mild”, “Moderate” and “Severe”, corresponding to scores of 5-6, 7-9 and 10-15, respectively." Addition of table under special dosage instructions titled "Modified assessment"		
				Deletion of text that read "Patients under 18 years: The safety and efficacy of Pegasys have not yet been established in these patients."		
				Addition of text under patients with renal impairment to read "For combination therapy with Pegasys + ribavirin the prescribing information for ribavirin must be precisely followed"		
				Addition of text to read "Children and adolescents: The safety and efficacy of Pegasys have not yet been established in patients under 18 years of age. Mode of administration: Subcutaneous administration.		
			Warnings and precautions	Deletion of text that read " In order to improve traceability of biologic medicinal products, the trade name Pegasys should be clearly recorded in the patient file. Substitution by any other biologic medicinal product requires the consent of the prescribing physician. Particulars in this prescribing information only applies to Pegasys."		

10	Pegasys	Peginterferon alfa-2a	Warnings and precautions	Revision of text under HCV/HIV-coinfected patients to read "Patients coinfected with HIV and receiving highly active antiretroviral therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should therefore be exercised when adding Pegasys and ribavirin to HAART therapy (see prescribing information for ribavirin). HCV/HIV-coinfected patients with advanced cirrhosis receiving HAART may also be at increased risk of hepatic decompensation and possibly death if treated with alfa interferons, including Pegasys, with or without ribavirin. During treatment, coinfected patients should be closely monitored, for signs and symptoms of hepatic decompensation (including ascites, encephalopathy, variceal bleeding, impaired hepatic synthetic function and Child-Pugh score >6 (see Contraindications). The Child-Pugh scoring may be affected by factors related to treatment (indirect hyperbilirubinemia caused by drugs such as atazanavir and indinavir) and not necessarily attributable to hepatic decompensation. Patients with Child-Pugh scores >6 not due to indirect hyperbilirubinemia must discontinue treatment."	19-Aug-21	Roche Products Ghana Ltd
				Addition of text under Use of peginterferon as long-term maintenance monotherapy (off-label use) to read "Caution is indicated when switching the treatment to a different pharmaceutical form and/or a different medicinal product with the same active substance. The patient should be monitored appropriately. This medicinal product contains benzyl alcohol. Benzyl alcohol may cause allergic reactions. Because of the risk of accumulation and toxicity (“metabolic acidosis”), large amounts should be used with caution and if absolutely necessary, particularly in subjects with impaired hepatic or renal function. This medicinal product contains less than 1 mmol of sodium (23 mg) per 0.5 ml prefilled syringe, i.e. it is virtually “sodium-free”. This medicinal product contains less than 1 mmol of sodium (23 mg) per 1 ml vial, i.e. it is virtually “sodium-free”."		
			Undesirable effects	Revision of text to read "Benign, malignant and unspecified neoplasms (including cysts and polyps)"		
				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. Healthcare professionals are asked to report any suspected new or serious adverse reaction."		

10	Pegasys	Peginterferon alfa-2a	Properties and effects	Addition of text to read "Hepatic impairment: The pharmacokinetic behaviour of Pegasys was similar in healthy subjects and patients with hepatitis B or C. The pharmacokinetic profiles and plasma concentrations of peginterferon alfa-2a are comparable in hepatitis C patients without and with cirrhosis (compensated, Child-Pugh A). No data are available on patients with decompensated liver disease (see “Contraindications”)."	19-Aug-21	Roche Products Ghana Ltd
				Deletion of text under renal impairment that read "In patients with end-stage renal disease undergoing hemodialysis, Pegasys clearance is reduced by 25%–45%, and first administration of a 135 µg dose results in exposure similar to that with a 180 µg dose in patients with normal renal function."		
			Other Information	Addition of text to include "Shelf life: Do not use this medicine after the expiry date (“EXP”) stated on the container. Special precautions for storage: Store in the refrigerator (2-8°C). Do not freeze. Keep the container in the outer carton in order to protect the contents from light. Keep out of the reach of children.		
				Addition of text to read "Disposal of unused or expired medicinal products: The improper release of medicinal products into the environment should be avoided wherever possible. Do not dispose of medicinal products via the waste water system and avoid disposal in domestic waste."		
11	Pharmorubicin	Epirubicin	Special warnings and precautions for use	Addition of text under cardiac function to include "There have been sporadic reports of fetal/neonatal cardiotoxic events including fetal death following in utero exposure to epirubicin (see Section 4.6)."	23-Feb-21	Pfizer
				Addition of text to in clude "Embryo-fetal toxicity: Epirubicin can cause genotoxicity. An effective method of contraception is required for both male and female patients during and for a period after treatment with epirubicin (see Section.6). Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available.		
			Fertility, pregnancy and lactation	Revision of text under impairment of fertlity to read "Men undergoing treatment with epirubicin should be advised to use effective contraceptive methods during treatment and for at least 3.5 months after the last dose"		

11	Pharmorubicin	Epirubicin	Fertility, pregnancy and lactation	Revision of text under pregnancy to read "Women of child-bearing potential should be advised to avoid becoming pregnant during treatment and to use effective contraceptive methods during treatment and for at least 6.5 months after last dose. There are no studies in pregnant women. Epirubicin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experimental data in animals suggest that epirubicin may cause fetal harm when administered to a pregnant woman. Avoid the use of epirubicin during the 1st trimester. Available human data do not establish the presence or absence of major birth defects and miscarriage related to the use of epirubicin during the 2nd and 3rd trimesters. If epirubicin is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. There have been sporadic reports of fetal and/or neonatal transient ventricular hypokinesia, transient elevation of cardiac enzymes, and of fetal death from suspected anthracycline-induced cardiotoxicity following in utero exposure to epirubicin in 2nd and/or 3rd trimesters (see Section 4.4). Monitor the fetus and/or neonate for cardiotoxicity and perform testing consistent with community standards of care".	23-Feb-21	Pfizer
				Revision of text under lactation to read "It is not known whether epirubicin is excreted in human milk. Because many drugs, including other anthracyclines, are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from epirubicin, advise lactating women not to breastfeed during treatment with epirubicin and for at least 7 days after last dose.		
12	Robestar	Rosuvastatin calcium	Interaction with other medicinal products and other forms of interaction	Addition of text to include " Do not take Robestar if you take a combination of medicines such as sofosbuvir/velpatasvir/voxilaprevir (used for treatment of chronic hepatitis C viral infections)	17-Aug-21	Sandoz Pharmaceuticals d.d.

12	Robestar	Rosuvastatin calcium	Warnings and precautions	Addition of text to include " Stevens-Johnson syndrome (serious blistering of the skin, mouth, eyes and genitals): Drug reaction with eosinophilia and systemic symptoms (extensive skin rash in association with internal organ involvement, lymph node enlargement, elevated white blood cells.) which could be life-threatening or fatal, have been reported with rosuvastatin. If signs and symptoms suggestive of this reaction appears, Robestar® should be stopped immediately and an alternative treatment should be considered."	17-Aug-21	Sandoz Pharmaceuticals d.d.
			Undesirable effects	Addition of text to include "Drug reaction with eosinophilia and systemic symptoms (extensive skin rash in association with internal organ involvement, lymph node enlargement, elevated white blood cells.)"		
13	Tecentriq	Atezolizumab	Posology and method of administration	Revision of text under dose modification advice table for tecentriq to read "Hepatitis in patients without hepatocellular carcinoma (HCC) "	09-Jul-21	Roche Products Ghana Ltd
				Addition of text under Hepatitis in patients without hepatocellular carcinoma (HCC) to include " Severity: If AST/ALT is within normal limits at baseline and increases to >3x to ?10x ULN or If AST/ALT is >1 to ?3x ULN at baseline and increases to >5x to ?10x ULN or If AST/ALT is >3x to ?5x ULN at baseline and increases to >8x to ?10x ULN; Treatment modification:Withhold Tecentriq . Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Severety:If AST/ALT increases to >10x ULN or total bilirubin increases to >3x ULN; Treatment modification:Permanently discontinue Tecentriq. "		

13	Tecentriq	Atezolizumab	Special warnings and precautions for use	Addition of text under immune-related hepatitis to include "For patients with HCC, treatment with atezolizumab should be withheld if ALT or AST increases to > 3 to ≤10 x ULN from normal limits at baseline, or > 5 to ≤10 x ULN from > 1 ULN to ≤3 x ULN at baseline, or > 8 to ≤10 x ULN from > 3 ULN to ≤5 x ULN at baseline, and persists for more than 5 to 7 days, and 1 to 2 mg/kg/day of prednisone or equivalent should be started. If the event improves to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued if ALT or AST increases to > 10 x ULN or total bilirubin increases > 3 x ULN)."	09-Jul-21	Roche Products Ghana Ltd
			Undesirable effect	Addition of text under infections and infestations to read "Common: Sepsis" for Atezolizumab in combination therapy		
				Addition of text under immune system disorders read "common:infusion-related reaction" for Atezolizumab in combination therapy		
				Addition of text under general disorders and administration site disorders to read " very common:oedema peripheral		
14	Uperio	Sacubitril/Valsartan	Therapeutic indication	Revision of text to read "UPERIO is indicated for the treatment of heart failure (NYHA class II-IV) in patients with reduced ejection fraction. Uperio has been shown to reduce the rate of cardiovascular death and heart failure hospitalization and to reduce the rate of all-cause mortality in these patients".	28-Jul-21	Pfizer
				Addition of text to read "Left ventricular ejection fraction (LVEF) is a variable measure, so use clinical judgment in deciding whom to treat [see Clinical Studies . Uperio is administered in place of an ACE inhibitor or ARB".		
			Overdosage	Revision of text to read " Limited data are available with regard to over dosage in human subjects with UPERIO. In healthy volunteers, a single dose of UPERIO 1200mg, and multiple doses of 900mg (14 days) have been studied and were well tolerated".		
			Clinical studies	Deletion of text that read "Dosing in clinical trials was based on the total amount of both components of UPERIO, i.e., 50 mg, 100 mg, and 200 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively".		

15	Xeloda	Capecitabine	Undesirable effect	Addition of text to include "Frequency not known: angioedema (observed in the post-marketing setting). "	19-Aug-21	Roche Products Ghana Ltd
16	Xigduo XR	Dapaglifozin/Metformin	Indications and Usage	Addition of text to read "Dapagliflozin is indicated to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors."	12-Nov-20	Astrazeneca
				Addition of text under recoomended dosage to include "To reduce the risk of hospitalization for heart failure, the recommended dose for dapagliflozin is 10 mg once daily."		
			Contraindication	Revision of text to read "History of a serious hypersensitivity reaction to dapagliflozin, such as anaphylactic reactions or angioedema, or hypersensitivity to metformin HCL".		
			Warnings and Precaution	Revision of subheading to read "Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues".		
				Deletion of texts that read "Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs."		
				Addition of text to include "Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. XIGDUO XR may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with XIGDUO XR."		
				Deletion of text that read "Increases in Low-Density Lipoprotein Cholesterol (LDL-C): Increases in LDL-C occur with dapagliflozin [see Adverse Reactions (6.1)]. Monitor LDL-C and treat per standard of care after initiating XIGDUO XR. "		

16	Xigduo XR	Dapaglifozin/Metformin	Warnings and Precaution	Deletion of text that read "Bladder Cancer: Across 22 clinical studies, newly diagnosed cases of bladder cancer were reported in 10/6045 patients (0.17%) treated with dapagliflozin and 1/3512 patient (0.03%) treated with placebo/comparator. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 4 cases with dapagliflozin and no cases with placebo/comparator. Bladder cancer risk factors and hematuria (a potential indicator of preexisting tumors) were balanced between treatment arms at baseline. There were too few cases to determine whether the emergence of these events is related to dapagliflozin. There are insufficient data to determine whether dapagliflozin has an effect on pre-existing bladder tumors. Consequently, XIGDUO XR should not be used in patients with active bladder cancer. In patients with prior history of bladder cancer, the benefits of glycemic control versus unknown risks for cancer recurrence with XIGDUO XR should be considered."	12-Nov-20	Astrazeneca
				Deletion of text that read "There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with XIGDUO XR".		
			Adverse reactions	Revision of text under clinical trial experience to read "Pool of 12 Placebo-Controlled Studies for Dapagliflozin 5 and 10 mg for Glycemic Control"		

16	Xigduo XR	Dapaglifozin/Metformin	Adverse reactions	Deletion of text that read "Impairment of Renal Function: Use of dapagliflozin was associated with increases in serum creatinine and decreases in eGFR (see Table 4). In patients with normal or mildly impaired renal function at baseline, serum creatinine and eGFR returned to baseline values at Week 24. Renal-related adverse reactions, including renal failure and blood creatinine increase, were more frequent in patients treated with dapagliflozin (see Table 5). Elderly patients and patients with impaired renal function were more susceptible to these adverse reactions (see Table 5). Sustained decreases in eGFR were seen in patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m2) In the pool of 12 clinical studies, a subgroup analysis assessed the safety of patients with eGFR between 30 to less than 60 mL/min/1.73 m2. At Week 24, the safety was similar to that seen in the overall program, although a higher proportion of patients had at least one event related to renal impairment or failure."	12-Nov-20	Astrazeneca
				Deletion of text that read "Fractures: In a study of patients with eGFR 30 to less than 60 mL/min/1.73 m2, 13 patients experienced bone fractures for treatment durations up to 104 weeks. No fractures occurred in the placebo group, 5 occurred in the dapagliflozin 5 mg group, and 8 occurred in the dapagliflozin 10 mg group. Eight of these 13 fractures were in patients who had a baseline eGFR of 30 to 45 mL/min/1.73 m2. Ten of the 13 fractures were reported within the first 52 weeks. There was no apparent pattern with respect to the anatomic site of fracture.		
				Addition of text to read " In the DECLARE study [see Clinical Studies (14.2)], severe events of hypoglycemia were reported in 58 (0.7%) out of 8574 patients treated with dapagliflozin 10 mg and 83 (1.0%) out of 8569 patients treated with placebo.		

16	Xigduo XR	Dapaglifozin/Metformin	Adverse reactions	Addition of text under genital mycotic infections to include "In the DECLARE study [see Clinical Studies (14.2)], serious genital mycotic infections were reported in <0.1% of patients treated with dapagliflozin 10 mg and <0.1% of patients treated with placebo. Genital mycotic infections that caused study drug discontinuation were reported in 0.9% of patients treated with dapagliflozin 10 mg and <0.1% of patients treated with placebo. Ketosis: In the DECLARE study [see Clinical Studies (14.2)], events of diabetic ketoacidosis (DKA) were reported in 27 out of 8574 patients in the dapagliflozin-treated group and in 12 out of 8569 patients in the placebo group. The events were evenly distributed over the study period."	12-Nov-20	Astrazeneca
				Addition of text under laboratory tests to include "Increases in Serum Creatinine and Decreases in eGFR. Dapagliflozin: Initiation of dapagliflozin causes an increase in serum creatinine and decrease in eGFR. In patients with normal or mildly impaired renal function at baseline, the serum creatinine and and eGFR returned to baseline at Week 24. Sustained decreases in eGFR were seen in patients with moderate renal impairment (eGFR 30 to less than 60 ml/min/1.73 m2) [see Mechanism of Action (12.1)]".		
				Deletion of text under laboratory tests that read "Increase in Serum Inorganic Phosphorus. Dapagliflozin: In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in dapagliflozin 10 mg–treated patients compared with placebo-treated patients (mean increases of 0.13 mg/dL versus −0.04 mg/dL, respectively). Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia (≥5.6 mg/dL if age 17-65 or ≥5.1 mg/dL if age ≥66) were reported in the dapagliflozin 10 mg group versus the placebo group at Week 24 (1.7% versus 0.9%, respectively)."		

16	Xigduo XR	Dapaglifozin/Metformin	Adverse reactions	Addition of text under "Increase in Low-Density Lipoprotein Cholesterol" to include "In the DECLARE study [see Clinical Studies (14.2)], mean changes from baseline after 4 years were 0.4 mg/dL versus -4.1 mg/dL for total cholesterol, and -2.5 mg/dL versus -4.4 mg/dL for LDL cholesterol, in dapagliflozin 10 mg-treated and the placebo groups, respectively. Dapagliflozin."	12-Nov-20	Astrazeneca
				Revision of text under Vitamin B12 concentrations to read "In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients".		
			Drug Interactions	Deletion of text that read" In healthy volunteers, the pharmacokinetics of metformin and propranolol, and of metformin and ibuprofen were not affected when coadministered in single-dose interaction studies".		
			Use in Special Population	Revision of text under geriatric use to read "In patients ≥65 years of age, a higher proportion of patients treated with dapagliflozin had adverse reactions of hypotension"		
				Deletion of text that read "although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney and because the risk of lactic acidosis with metformin is greater in patients with moderately to severely impaired renal function.		
				Deletion of text under renal impairment that read "In clinical studies dapagliflozin was associated with increases in serum creatinine and decreases in eGFR"		
				Addition of text under renal impairment to include "Patients with renal impairment using dapagliflozin for glycemic control may also be more likely to experience hypotension and may be at higher risk for acute kidney injury. In the study of patients with an eGFR 30 to less than 60 mL/min/1.73 m2, 13 patients receiving dapagliflozin experienced bone fractures compared to none receiving placebo.		
			Overdosage	Deletion of text that read "Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established".		

16	Xigduo XR	Dapaglifozin/Metformin	Clinical Pharmacology	Addition of text under mechanism of action to include "Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, lowering both pre- and afterload of the heart and downregulation of sympathetic activity".	12-Nov-20	Astrazeneca
			Clinical Studies	Addition of text to include "Section 14.2 Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus Dapagliflozin Effect on Cardiovascular Events (DECLARE, NCT01730534) was an international, multicenter, randomized, double-blind, placebocontrolled, clinical study conducted to determine the effect of dapagliflozin 10 mg relative to placebo on CV outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either established CVD or two or more additional CV risk factors (age ≥55 years in men or ≥60 years in women and one or more of dyslipidemia, hypertension, or current tobacco use).Concomitant antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases. Of 17160 randomized patients, 6974 (40.6%) had established CVD and 10186 (59.4%) did not have established CVD. A total of 8582 patients were randomized to dapagliflozin 10 mg, 8578 to placebo, and patients were followed for a median of 4.2 years."		

16	Xigduo XR	Dapaglifozin/Metformin	Clinical Studies	Addition of text to include "Approximately 80% of the trial population was White, 4% Black or African-American, and 13% Asian. The mean age was 64 years, and approximately 63% were male. Mean duration of diabetes was 11.9 years and 22.4% of patients had diabetes for less than 5 years. Mean eGFR was 85.2 mL/min/1.73 m2. At baseline, 23.5% of patients had microalbuminuria (UACR ≥30 to ≤300 mg/g) and 6.8% had macroalbuminuria (UACR >300mg/g). Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m2. At baseline, 10% of patients had a history of heart failure. Most patients (98.1%) used one or more diabetic medications at baseline. 82.0% of the patients were being treated with metformin, 40.9% with insulin, 42.7% with a sulfonylurea, 16.8% with a DPP4 inhibitor, and 4.4% with a GLP-1 receptor agonist. Approximately 81.3% of patients were treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, 75.0% with statins, 61.1% with antiplatelet therapy, 55.5% with acetylsalicylic acid, 52.6% with beta-blockers, 34.9% with calcium channel blockers, 22.0% with thiazide diuretics, and 10.5% with loop diuretics. A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio (HR) of the composite of CV death, myocardial infarction (MI), or ischemic stroke and to test for superiority on the dual primary endpoints: the composite of hospitalization for heart failure or CV death, and MACE, if non-inferiority was demonstrated".	12-Nov-20	Astrazeneca

16	Xigduo XR	Dapaglifozin/Metformin	Clinical Studies	Addition of text to include "The incidence rate of MACE was similar in both treatment arms: 2.3 MACE events per 100 patient years on dapagliflozin vs. 2.46 MACE events per 100 patient years on placebo. The estimated hazard ratio of MACE associated with dapagliflozin relative to placebo was 0.93 with a 95.38% confidence interval of (0.84,1.03). The upper bound of this confidence interval, 1.03, excluded a risk margin larger than 1.3. Dapagliflozin 10 mg was superior to placebo in reducing the incidence of the primary composite endpoint of hospitalization for heart failure or CV death (HR 0.83 [95% CI 0.73, 0.95]). The treatment effect was due to a significant reduction in the risk of hospitalization for heart failure in subjects randomized to dapagliflozin 10 mg (HR 0.73 [95% CI 0.61, 0.88]), with no change in the risk of CV death (Table 14 and Figures 4 and 5). Table 14: Treatment Effects for the Primary Endpoints* and Their Components* in the DECLARE Study Figure 4: Time to First Occurrence of Hospitalization for Heart Failure or CV Death in the DECLARE Study Figure 5: Time to First Occurrence of Hospitalization for Heart Failure in the DECLARE Study."	12-Nov-20	Astrazeneca
			Patient Counselling information	Addition of text under hypersensitivity reactions to include "anaphylatic reaction"		
				Deletion of text that read "Bladder Cancer Inform patients to promptly report any signs of macroscopic hematuria or other symptoms potentially related to bladder cancer".		
				Addition of text to include "Missed Dose If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of XIGDUO XR at the same time."		
17	Zavicefta	Ceftazidime/Avibactam	Therapeutic indications	Revision of text to read "Zavicefta is indicated in adults, infants (aged 3 months and older), children, and adolescents for the treatment of the following infections"	23-Feb-21	Pfizer

17	Zavicefta	Ceftazidime/Avibactam	Therapeutic indications	Revision of text to read " Complicated Intra-Abdominal Infection (cIAI) (in combination with metronidazole) . Revision of texts to read "Zavicefta is indicated in adults, infants (aged 3 months and older), children, and adolescents for the treatment of the following infections"	23-Feb-21	Pfizer
				Addition of text to include "Treatment of adult patients with bacteraemia that occurs in association with, or is suspected to be associated with cIAI, cUTI, or HAP/VAPRevision of texts to read " Complicated Intra-Abdominal Infection (cIAI) (in combination with metronidazole)		
			Posology and method of administration	Addition of subheading to read "Dosage in Adults with Creatinine Clearance (CrCL > 50 mL/min)"		
				Revision of text under treatment duration of Complicated Urinary Tract Infection (cUTI), including Pyelonephritis to read "The total duration of treatment could be increased to 14 days for patients with bacteraemia"		
				Addition of text to read "Bacteraemia associated, or suspected to be associated with the above infections: Duration of treatment should be in accordance with the site of infection".		
				Addition of text to read " To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process. To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process		
				Addition of text to read "Dosage in paediatric patients with creatinine clearance (CrCL) > 50 mL/min/1.73 m2 The recommended dosage of Zavicefta in paediatric patients (3 months to < 18 years) is based on the age and weight of the patient. Zavicefta is administered every 8 hours by intravenous infusion over 2 hours, see Table 2. The duration of therapy should be guided by the severity, site of infection and the patient's clinical and bacteriological progress".		
				Insertion of tabel to read "Table 2-Dosage in paediatric patients with CrCL > 50 mL/min/1.73 m2"		

17	Zavicefta	Ceftazidime/Avibactam	Posology and method of administration	Addition of text under table 2 to include "To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process. b. To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process. c. Treatment duration includes intravenous plus oral treatment. d .There is very limited experience with the use of Zavicefta for more than 14 days. *Calculated using the Schwartz bedside formula for paediatric patients (mL/min/1.73 m2"	23-Feb-21	Pfizer
				Insertion of tables 3 and 4		
				Addition of text to read "There is insufficient information to recommend a dosage regimen for paediatric patients < 2 years of age that have a CrCL < 16 mL/min/1.73 m2".		
				Additionof text under paediatric patient to read "Safety and efficacy in paediatric patients < 3 months old have not been established".		
				Revision of text under method of administration to read "Zavicefta is administered to adults by intravenous infusion over 1 2 hours in an appropriate infusion volume (see section 6.6). For paediatric patients, the infusion volume may be adjusted (see section 6.6).		
			Special warnings and precautions for use	Addition of text under limitation of the clinical data to read "No clinical studies have been conducted in paediatric patients with nosocomial pneumonia. The efficacy of ceftazidime/avibactam for the treatment of paediatric patients ≥ 3 months of age with HAP/VAP is extrapolated from adults and is based on analyses of the pharmacokinetic-pharmacodynamic relationship for ceftazidime/avibactam and on paediatric experience with ceftazidime alone (see section 5.2)".		
			Undesirable effect	Insertion of table 5 and table heading to read "Adverse Drug Reaction Table"		
				Addition of subheading and texts to read "Paediatric population: The safety assessment in paediatric patients is based on the safety data from two trials in which 61 patients with cIAI (aged from 3 years to less than 18 years) and 67 patients with cUTI (aged from 3 months to less than 18 years) received TRADENAME. Overall, the safety profile in these 128 paediatric patients was similar to that observed in the adult population with cIAI and cUTI.		

17	Zavicefta	Ceftazidime/Avibactam	Pharmacologic properties	Addition of text under pharmacodynamic properties, Table 9 to read "Among patients with baseline bacteraemia who were enrolled in any of the phase 3 cIAI studies (RECLAIM, RECLAIM3 or REPRISE), clinical response at TOC in the subset of patients with bacteraemia due to aerobic Gram-negative pathogens was observed in 9/11 (81.8%) patients treated with CAZ-AVI + MTZ and 9/10 (90.0%) patients treated with comparators (meropenem or best-available therapy). The most common Gram-negative baseline pathogens isolated from the blood were E. coli and P. aeruginosa. A favorable per-pathogen microbiological response at TOC was reported in 9/11 (81.8%) CAZ-AVI- and 6/6 (100.0%) comparator-treated patients with E. coli bacteraemia; and 3/4 (75.0%) CAZ-AVI- and 2/2 (100.0%) comparator-treated patients with P. aeruginosa bacteraemia". Addition of text under pharmacodynamic to read "For HAP/VAP patients enrolled with baseline bacteraemia, clinical cure at TOC in the subset of patients with bacteraemia due to aerobic Gram-negative pathogens was observed in 10/15 (66.7%) patients treated with CAZ-AVI and 5/8 (62.5%) patients treated with meropenem. Although patient numbers were small for any given pathogen, favourable per-pathogen microbiological response rates in this sub-group were broadly similar to those of the overall population. Among patients enrolled with baseline bacteraemia in the Phase 3 program across all indications combined (cIAI, cUTI or HAP/VAP), clinical cure at TOC in the subset of patients with bacteraemia due to aerobic Gram-negative pathogens was observed in 47/54 (87.0%) patients treated with CAZ-AVI ± MTZ and 39/47 (83.0%) patients treated with comparators. For the two most commonly occurring pathogens in this sub-group, a favourable per-pathogen microbiological response at TOC was reported in 32/37 (86.5%) CAZ-AVI ± MTZ- and 29/33 (87.9%) comparator treated patients with E. coli bacteraemia; and 6/11 (54.5%) CAZ-AVI ± MTZ- and 3/6 (50.0%) comparator treated patients with P. aeruginosa bacteraemia."	23-Feb-21	Pfizer

17	Zavicefta	Ceftazidime/Avibactam	Pharmacologic properties	Addition of text under pharmacodynamics to read "Paediatric population Ceftazidime-avibactam has been evaluated in paediatric patients aged 3 months to < 18 years in two Phase 2 single blind, randomized, comparative clinical studies, one in patients with cIAI and one in patients with cUTI (Doses provided in table 2). Patients aged ≥ 3 months to < 1 year must have been born at term (defined as gestational age ≥ 37 weeks). Patients treated with ceftazidime-avibactam in the cIAI trial also received metronidazole (administered per local label; suggested dose: 10 mg/kg every 8 hours, administered IV over 20 to 30 minutes). The primary objective in each study was to assess safety and tolerability of ceftazidime-avibactam (+/- metronidazole). Secondary objectives included assessment of PK and efficacy; efficacy was a descriptive endpoint in both studies. Addition of text under pharmacodynamics to read "cIAI: A total of 83 paediatric patients with cIAI were randomized (3:1) and received treatment with either ceftazidime avibactam plus metronidazole (n=61) (doses provided in table 2), or meropenem (n=22), 20 mg/kg IV every 8 hours. After a minimum of 72 hours of IV treatment, there was an optional switch to oral therapy for patients who had clinical improvement, as defined in the study protocol. The total duration of antibiotic therapy (IV plus oral) was between 7 and 15 days. TOC assessments were performed 8 to 15 days after the last dose of study drug (IV or oral). The majority of patients (87%) had appendiceal perforation or peri-appendiceal abscess (52/61, 85.2% ceftazidime avibactam plus metronidazole; 20/22, 90.9% meropenem). The CE population included patients who had a confirmed diagnosis of cIAI and received a minimum duration of IV study drug, and excluded patients who had a clinical response of indeterminate and/or an important protocol deviation impacting the assessment of efficacy. The microbiological intent-to treat (micro-ITT) population included 69 patients (50 ceftazidime-avibactam plus metronidazole, 19 meropenem) who had at least one baseline intra-abdominal pathogen. Favourable clinical response rates at TOC are presented in Table 15." Insertion of tables to include "table 15, 16, 17 and Table 18"	23-Feb-21	Pfizer

17	Zavicefta	Ceftazidime/Avibactam	Pharmacologic properties	Addition of text under pharmacokinetic properties, paediatric patients to include "The pharmacokinetics of ceftazidime and avibactam were evaluated in paediatric patients from 3 months to < 18 years of age with suspected or confirmed infections following a single dose of ceftazidime 50 mg/kg and avibactam 12.5 mg/kg for patients weighing < 40 kg or Zavicefta 2 g/0.5 g (ceftazidime 2 grams and avibactam 0.5 grams) for patients weighing ≥ 40 kg. Plasma concentrations of ceftazidime and avibactam were similar across all four age cohorts in the study (3 months to < 2 years, 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years). Ceftazidime and avibactam AUC0-t and Cmax values in the two older cohorts (children from 6 to < 18 years), which had more extensive pharmacokinetic sampling, were similar to those observed in healthy adult subjects with normal renal function that received TRADENAME 2g/0.5g. Data from this study and the two Phase 2 paediatric studies in patients with cIAI and cUTI were pooled with PK data from adults (Phase 1 to Phase 3) to update the population PK model, which was used to conduct simulations to assess PK/PD target attainment. Results from these simulations demonstrated that the recommended dose regimens for paediatric patients with cIAI, cUTI and HAP/VAP, including dose adjustments for patients with renal impairment, result in systemic exposure and PK/PD target attainment values that are similar to those in adults at the approved TRADENAME dose of 2 g/0.5 g administered over 2 hours, every 8 hours.	23-Feb-21	Pfizer

17	Zavicefta	Ceftazidime/Avibactam	Pharmacologic properties	Addition of text under pharmacokinetic properties, paediatric patients to include "There is limited experience with the use of ceftazidime plus avibactam in the paediatric groups of 3 months to < 6 months. The recommended dosing regimens are based on simulations conducted using the final population PK models. Simulations demonstrated that the recommended dose regimens result in comparable exposures to other age groups with PK/PD target attainment > 90%. Based on data from the completed paediatric clinical trials, at the recommended dose regimens, there was no evidence of over or under exposure in the subjects aged 3 months to < 6 months. There is limited experience with the use of ceftazidime plus avibactam in the paediatric groups of 3 months to < 6 months. The recommended dosing regimens are based on simulations conducted using the final population PK models. Simulations demonstrated that the recommended dose regimens result in comparable exposures to other age groups with PK/PD target attainment > 90%. Based on data from the completed paediatric clinical trials, at the recommended dose regimens, there was no evidence of over or under exposure in the subjects aged 3 months to < 6 months. In addition, there is very limited data in paediatric patients aged 3 months to < 2 years with impaired renal function (CrCL ≤ 50 mL/min/1.73 m2), with no data in severe renal impairment from the completed paediatric clinical trials. Population PK models for ceftazidime and avibactam were used to conduct simulations for patients with impaired renal function".	23-Feb-21	Pfizer
			Pharmaceutical properties	Revision of text under incompatibilities to read "The compatibility of Zavicefta with other medicines has not been established. Zavicefta should not be mixed with or physically added to solutions containing other medicinal products except diluents mentioned in section 6.6."		

17	Zavicefta	Ceftazidime/Avibactam	Pharmaceutical particulars	Addition of text under shelf life to include "Infusion syringes: The chemical and physical in-use stability has been demonstrated for up to 6 hours at room temperature 15 25°C. From a microbiological point of view, the medicinal product should be used immediately, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and must not exceed 6 hours at room temperature 15 25°C."	23-Feb-21	Pfizer
				Revision of text under special precautions for disposal and other handling to read "The reconstituted solution must be used to prepare the final infusion solution within 30 minutes from initial vial puncture.		
				Addition of text to include " Zavicefta (ceftazidime/avibactam) is a combination product; each vial contains 2 g of ceftazidime and 0.5 g of avibactam in a fixed 4:1 ratio. Dosage recommendations are based on the ceftazidime component only".		

17	Zavicefta	Ceftazidime/Avibactam	Pharmaceutical particulars	Addition and revision of text to read "Instructions for preparing adult and paediatric doses in INFUSION BAG or in INFUSION SYRINGE: NOTE: The following procedure describes the steps to prepare an infusion solution with a final concentration of 8 40 mg/mL of ceftazidime. 1. Prepare the reconstituted solution (167.3 mg/mL of ceftazidime): a) Insert the syringe needle through the vial closure and inject 10 mL of sterile water for injections. b) Withdraw the needle and shake the vial to give a clear solution. c) Insert a gas relief needle through the vial closure after the product has dissolved to relieve the internal pressure (this is important to preserve product sterility). 2. Prepare the final solution for infusion (final concentration must be 8-40 mg/mL of ceftazidime): a) Infusion bag: Further dilute the reconstituted solution by transferring an appropriately calculated volume of the reconstituted solution to an infusion bag containing any of the following: sodium chloride 9 mg/mL (0.9%) solution for injection, dextrose 50 mg/mL (5%) solution for injection, sodium chloride 4.5 mg/mL and dextrose 25 mg/mL solution for injection (0.45% sodium chloride and 2.5% dextrose) or Lactated Ringer's solution. b) Infusion syringe: Further dilute the reconstituted solution by transferring an appropriately calculated volume of the reconstituted solution combined with a sufficient volume of diluent (sodium chloride 9 mg/mL (0.9%) solution for injection or dextrose 50 mg/mL (5%) solution for injection) to an infusion syringe." Insertion of a table to read " Table 19"	23-Feb-21	Pfizer