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	Daktacort	Miconazole nitrite / Hydrocortisone	What you need to know before you use Daktacort cream	Addition of text "Talk to your doctor if there is a worsening of your condition during use of Daktacort. You may be experiencing an allergic reaction, have an infection or your condition requires a different treatment. If you experience a recurrence of your condition shortly after stopping treatment, within 2 weeks, do not restart using the cream without consulting your doctor unless your doctor has previously advised you to do so. If your condition has resolved and on recurrence the redness extends beyond the initial treatment area and you experience a burning sensation, please seek medical advice before restarting treatment. Keep this medicine away from your eyes. If you get any cream in your eyes, rinse with water straight away. Keep your eyes open when you rinse."Under Sub tilte Warnings and precautions	21/11/2022	Janssen
			Possible side effects	Addition of text " Steroid withdrawal reaction: If used continuously for prolonged periods awithdrawal reaction may occur on stopping treatment with some or all of thefollowing features: redness of the skin which can extend beyond the initialarea treated, a burning or stinging sensation, intense itching, peeling of the skin, oozing open sores." Under sub title frequency not known.		
2	Durogesic	Fentanyl	Contents of the pack and other	Deletion of sub heading "DUROGESIC 75 µg/hour " Under sub title Information Deletion of text "The active substance in DUROGESIC is fentanyl. Each patch contains 12.6 mg of fentanyl, which delivers a dose of 75 micrograms/hour." Under sub section information	22/11/2022	Janssen
			Other ingredients in the patch are:	Deletion of text to read " The DUROGESIC 75 micrograms/hour patch also contains blue printing ink.		
			What DUROGESIC looks like and contents of the pack	Deletion of text "DUROGESIC 75 µg/hour. DUROGESIC is a translucent rectangular patch with rounded corners. Each patch is 31.5 cm2, and is marked with a border and “DUROGESIC 75 µg fentanyl/h” in blue printing ink."		
3	Diprivan Injection 1% and 2%	Propofol 10mg and 20mg	Undesirable effects	Addition of text to include under sub table summary of adverse reactions" The following convention has been utilised for the classification of frequency: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥ 1/10,000 and <1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data)." Addition of "Not known (cannot be estimated from the avaialble data" with frequency very rare (< 1/10,000) under the System Organ Class Reproductive system and breast disorders with event Priapism	18/11/2022	Kama

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Diprivan Injection 1% and 2%	Propofol 10mg and 20mg	Interaction with other medicinal products and other forms of interaction	Addition of text "Diprivan has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking drugs, inhalational agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of Diprivan may be required where general anaesthesia or sedation is used as an adjunct to regional anaesthetic techniques. Profound hypotension has been reported following anaesthetic induction with propofol in patients treated with rifampicin. The hypotensive effect of Diprivan may be potentiated by the concomitant administration of opiate analgesics. This effect may be more marked in elderly patients and when agents such as alfentanil are given by infusion. A need for lower propofol doses has been observed in patients taking midazolam. The co-administration of propofol with midazolam is likely to result in enhanced sedation and respiratory depression. When usedconcomitantly, a dose reduction of propofol should to be considered."	18/11/2022	Kama
			Special warnings and special precautions for use	Addition of text to include“As with other intravenous anaesthetic agents, caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic or debilitated patients.”		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Ganfort	Bimatoprost 0,3 mg and timolol maleate 5mg	Special warnings and precautions for use	Revision of text "The components of GANFORT may beabsorbed systemically. Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-blockers may occur. To reduce systemic absorption, see section 4.2 Cardiac disorders: In patients with cardiovascular diseases (e.g. coronary artery disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers, as in GANFORT should be critically assessed and therapy with other active substances should be considered. GANFORT should be used with caution in patients with cardiovascular disease (e.g. coronary heart disease, Prinzmetal's angina, first degree heart block and cardiac failure) and hypotension. Patients with cardiovascular diseases should be monitored for signs of deterioration of these diseases, and of adverse reactions. Due to its negative effect on conduction time, GANFORT should only be given with caution to patients with first degree heart block. Vascular disorders: Patients with severe peripheral circulatory disturbances/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution. Respiratory disorders: Cardiac and respiratory reactions, including death due to bronchospasm in patients with asthma, and, rarely, death in association with cardiac failures have been reported following administration of timolol maleate, as in GANFORT. GANFORT should be used with caution in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk. Endocrine disorders: Timolol, as in GANFORT should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) as beta-blockers may mask the signs or symptoms of acute hypoglycaemia. Beta-blockers may also mask the signs of hyperthyroidism.	5/12/2022	Allergan Pharmaceuticals (Pty) Ltd

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Ganfort	Bimatoprost 0,3 mg and timolol maleate 5mg	Special warnings and precautions for use	Revision of text "The components of GANFORT may be absorbed systemically. Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-blockers may occur. To reduce systemic absorption, see section 4.2 Cardiac disorders: In patients with cardiovascular diseases (e.g. coronary artery disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers, as in GANFORT should be critically assessed and therapy with other active substances should be considered. GANFORT should be used with caution in patients with cardiovascular disease (e.g. coronary heart disease, Prinzmetal's angina, first degree heart block and cardiac failure) and hypotension. Patients with cardiovascular diseases should be monitored for signs of deterioration of these diseases, and of adverse reactions. Due to its negative effect on conduction time, GANFORT should only be given with caution to patients with first degree heart block. Vascular disorders: Patients with severe peripheral circulatory disturbances/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution. Respiratory disorders: Cardiac and respiratory reactions, including death due to bronchospasm in patients with asthma, and, rarely, death in association with cardiac failures have been reported following administration of timolol maleate, as in GANFORT. GANFORT should be used with caution in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk. Endocrine disorders: Timolol, as in GANFORT should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) as beta-blockers may mask the signs or symptoms of acute hypoglycaemia. Beta-blockers may also mask the signs of hyperthyroidism. Anaphylactic reactions: While taking timolol, as in GANFORT, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to a repeated challenge with such allergens and unresponsive to the usual dose of (epinephrine) adrenaline used to treat anaphylactic reactions. Choroidal detachment: Choroidal detachment has been reported with administration of aqueous suppressant therapy such as timolol, after filtration procedures.	5/12/2022	Allergan Pharmaceuticals (Pty) Ltd

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Ganfort	Bimatoprost 0,3 mg and timolol maleate 5mg	Special warnings and precautions for use	Surgical anaesthesia: Ophthalmic beta-blockers may impair compensatory tachycardia and increase risk of hypotension when used in conjunction with anaesthetics. Timolol, such as in GANFORT, may block systemic beta-agonist effects e.g. of epinephrine (adrenaline). The anaesthesiologist should be informed when the patient is receiving GANFORT. Hepatic: In patients with a history of mild liver disease or abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin at baseline, bimatoprost had no adverse reactions on liver function over 24 months. There are no known adverse reactions of ocular timolol, as in GANFORT, on liver function. Ocular: Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation since these have been observed during treatment with GANFORT. Some of these changes may be permanent and may lead to differences in appearance between the eyes if only one eye is treated. After discontinuation of GANFORT, pigmentation of iris may be permanent. After 12 months treatment with GANFORT, the incidence of iris pigmentation was 0,2 %. After 12 months treatment with bimatoprost eye drops alone, the incidence was 1,5 % and did not increase following 3 years treatment. Macular oedema, including cystoid macular oedema has been reported during treatment with GANFORT. GANFORT should be used with caution in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy). GANFORT should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated. Skin: There is a potential for hair growth to occur in areas where GANFORT solution comes repeatedly in contact with the skin surface. Thus, it is important to apply GANFORT as instructed and avoid it running onto the cheek or other skin areas. Excipients: The preservative in GANFORT, benzalkonium chloride, may cause eye irritation and may also be absorbed by soft contact lenses. Contact lenses must be removed prior to application, with at least a 15-minutes wait before reinsertion. Benzalkonium chloride is known to discolor soft contact lenses. Contact with soft contact lenses must be avoided. Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Therefore, monitoring is required with frequent or prolonged use of GANFORT in dry eye patients or where the cornea is compromised. As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medicines over an extended period, in patients with extensive ocular surface disease. In studies in patients with glaucoma or ocular hypertension with bimatoprost ophthalmic solution 0,03 %, it has been shown that more frequent exposure of the eye to more than one dose of bimatoprost (as in GANFORT) daily may decrease the IOP-lowering effect. Patients using GANFORT with other prostaglandin analogues should be monitored for changes to their intraocular pressure."	5/12/2022	Allergan Pharmaceuticals (Pty) Ltd

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Ganfort	Bimatoprost 0,3 mg and timolol maleate 5mg	Effects on ability to drive and use machines	Addition of text to include "Transient blurred vision may occur at installation, therefore the patient should wait until the vision clears before driving or using machinery."	5/12/2022	Allergan Pharmaceuticals (Pty) Ltd
			Undesirable effects	Addition of subtitle to read "Summary of the safety profile" Addition of subtitle "Tabulated summery of adverse reactions" Revision of text to include "Table 1 presents the adverse reactions that have been reported during clinical studies with all GANFORT formulations (GANFORT multi-dose and bimatoprost/timolol single-dose formulation) (within each frequency grouping, adverse reactions are presented in order of decreasing seriousness) or in the post-marketing period. The frequency is defined as follows: Very Common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥ 1/1 000 to < 1/100); Rare (≥ 1/10 000 to < 1/1 000); Very Rare (< 1/10 000); Not known (cannot be estimated from available data)." Revision of "Conjunctival hyperaemia, growth of eyelashes" with frequency very common under the System Organ Class eye disorders Revision of "Superficial punctate keratitis, corneal erosion, burning sensation, conjunctival irritation, eye pruritus, stinging sensation in the eye, foreign body sensation, dry eye, eyelid erythema, eye pain, photophobia, eye discharge, visual disturbance, eyelid pruritus, visual acuity worsened, blepharitis, eyelid oedema, eye irritation, lacrimation increased" with frequency common under the System Organ Class eye disorders Revision of "Iritis, conjunctival oedema, eyelid pain, abnormal sensation in the eye, asthenopia, trichiasis, iris hyperpigmentation, periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of eyelid sulcus, eyelid ptosis, enophthalmos, lagophthalmos and eyelid retraction, eyelash discolouration (darkening)1, epiphora" with frequency uncommon under the System Organ Class eye disorder Revision of "Cystoid macular oedema, eye swelling, blurred vision, ocular discomfort" with frequency not known under the System Organ Class eye disorder. Revision of "Blepharal pigmentation, hirsutism, periocular skin hyperpigmentation" with frequency common under the System Organ Class skin and subcutaneous tissue disorders Addition of "Alopecia, periocular skin discolouration" with frequency not known under the System Organ Class skin and subcutaneous tissue disorders Revision of text "Fatigue" with frequency not known under the System Organ Class General disorders and administration site conditions		
			Description of selected adverse reactions	Addition of "Adverse reactions reported in phosphate containing eye drops. Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Madopar	Levodopa, benserazide as benserazide hydrochloride.	Indications/Use	Revison of text to read under sub title Parkinson's disease "Madopar is indicated for the treatment of all forms of Parkinson's syndrome with the exception of drug-induced parkinsonism. " Revison of text to read under restless legs syndrome "Madopar is indicated for the treatment of idiopathic and symptomatic restless legs syndrome."	3/11/2022	Roche Ltd
			Dosage / Administration	Revison of text to read under sub title mode of administration "When taking Madopar capsules or Madopar DR tablets, patients must always ensure that they swallow the whole capsule or tablet without chewing it. Madopar DR tablets can be split into halves. Standard Madopar tablets can be broken into pieces to facilitate swallowing. Madopar LIQ is dissolved in a quarter of a glass of water (approx. 25-50 ml), but not in fruit juices, milk or hot beverages. The tablets disintegrate spontaneously, producing a milky-white suspension within a few minutes. Because this suspension rapidly sediments, it is advisable to stir the solution immediately before drinking. Madopar LIQ should be taken within half an hour of dissolving the tablet. When switching from standard Madopar to Madopar LIQ, the difference in pharmacokinetics (more rapid absorption) must be taken into account. The dosage and dosage interval must be carefully titrated in each patient; this applies also to elderly patients."		
			Special dosage instructions	Revision and deletion of text to read "The dose should Dosage must be carefully adjustedtitrated in all patients. Non-levodopa-based antiparkinsonian agents can continue to be given until the full therapeutic effect of Madopar is reachedapparent; after onset of the effect, however, they can often be gradually reduced. 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. 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. Due to the pharmacokinetic properties of Madopar HBS, the onset of action is approximately three hours. If desired, effective plasma levels may be achieved more rapidly by administering Madopar HBS together with Madopar Dispersible tablets or conventional capsules or tablets. This may prove especially useful for the first morning dose, which should preferably be somewhat higher than the subsequent daily doses.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Madopar	Levodopa, benserazide as benserazide hydrochloride.	Special dosage instructions	The individual dosage of Madopar HBS should be established slowly and carefully, with intervals of at least two to three days between each change of dosage. In patients with nocturnal disability, positive effects have been reported after gradually increasing the last evening dose up to 3 capsules Madopar HBS at bedtime. Revision of text to read under sub tittle patients with hepatci impairment "The safety and efficacy of Madopar have not been studied in patients with hepatic impairment (see “Contraindications” and “Pharmacokinetics/Kinetics in specific patient groups")." Revison of text to read under sub tittle patients with renal impairment "No dose adjustment of Madopar is required in patients with moderate renal impairment (creatinine clearance >30 ml/min) (see “Pharmacokinetics/Kinetics in specific patient groups”). Revision of text to read "Madopar is contraindicated for use in patients under 25 years of age."under sub heading children and adolescents Revision of text to read "Madopar is taken one hour before retiring. To prevent gastrointestinal upsets, it is best taken with a low-protein snack. Large, protein-rich meals should be carefully monitored for possible psychiatric sideavoided before administration. Madopar is generally taken over a prolonged period. The maximum daily dose should not exceed 500 mg Madopar." Revision of text to read "To prevent deterioration (i.e. onset of RLS symptoms early in the day, exacerbation of symptoms and involvement of other body regions), the maximum recommended daily dose of Madopar should not be exceeded. If RLS increases in frequency, it is important not to exceed the maximum daily dose of Madopar."	3/11/2022	Roche Ltd

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Madopar	Levodopa, benserazide as benserazide hydrochloride.	Usual dosage	Revision of text to read " The dosage of Madopar is based on the severity of the restless legs syndrome, the optimal effect being determined by gradual, individualised dose titration. RLS with sleep-onset insomnia: Unless otherwise prescribed, treatment of symptoms, particularly difficulty getting to sleep, is initiated with a dose of 62.5 to 125 mg of standard Madopar or Madopar LIQ in the evening before retiring. If symptoms persist, the dosage can be increased to two doses of 125 mg. RLS with sleep-onset and sleep-maintenance insomnia: In patients with restless legs symptoms and disturbed sleep during the night, half a Madopar DR sustained-release tablet is taken one hour before retiring. If this does not result in a satisfactory improvement in symptoms during the second half of the night, the dose can be increased to one Madopar DR sustained-release tablet. RLS with sleep-onset and sleep-maintenance insomnia at night and additional symptoms during the day: For daytime symptoms, one to two Madopar 125 mg capsules or tablets or Madopar LIQ tablets may be taken as required, bearing in mind that the total dose over 24 hours should not exceed 500 mg. Possible treatment failure could be due to interaction with meals. RLS due to dialysis-dependent renal failure: Dialysis patients with uraemic restless legs symptoms should take one to two Madopar 125 mg capsules or tablets or Madopar LIQ tablets as required 30 minutes before dialysis. Dose adjustment following undesirable effects./interactions In the event of deterioration or rebound, adjunctive therapy should be considered and the levodopa dose reduced; it may be necessary to gradually withdraw levodopa and replace it with a different drug."	3/11/2022	Roche Ltd

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Madopar	Levodopa, benserazide as benserazide hydrochloride.	Contraindications	Revision of text to read " • Hypersensitivity to any of theirthe ingredients. • Madopar must not be coadministeredTreatment with nonselectivenon-selective monoamine oxidase (MAO) inhibitors. Coadministration with or a combination of selective MAO-A and MAO-B inhibitors such as selegiline or rasagiline or with selective MAO-A inhibitors such as moclobemide is not contraindicated. Combination of a selective MAO-A inhibitor and a selective MAO-B inhibitor is equivalent to nonselective MAO inhibition and should therefore not be used at the same time as Madopar (see due to the risk of hypertensive crisis (see "Interactions)." • Madopar must not be given to patients with severely decompensatedDecompensated endocrine, renal, (other than RLS patients on dialysis) or hepatic or cardiac disorders, or to thosedysfunction. • Cardiac disorder. • Psychiatric disease with a psychiatric illness comprising a psychotic component. • Madopar must not be given to patients underPatients less than 25 years of ageold (skeletal development may notmust be complete). Madopar is contraindicated in patients with closed • Closed-angle glaucoma. • Madopar must not be given to pregnant women or toPregnancy and women of childbearing potential in the absence of adequate contraception. If pregnancy occurs in a woman taking Madopar, the medicinedrug must be discontinued as instructedwithdrawn, bearing in mind the factors mentioned under "Warnings and Precautions.precautions". The modemanner of treatment withdrawal shouldmust be decided on a case-by-casean individual basis.	3/11/2022	Roche Ltd

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Madopar	Levodopa, benserazide as benserazide hydrochloride.	Warnings and precautions	Revision of text under General sub tittle Warnings related to immunological reactions "Hypersensitivity reactions can occur in susceptible individuals." Revision of text to read under General "Madopar must not be withdrawn abruptly. Abrupt withdrawal of the preparation may result in a potentially life-threatening neuroleptic malignant-like syndrome (hyperpyrexia and muscular rigidity, possibly psychological changes and elevated serum creatine phosphokinase). Should such symptoms and signs occur, the patient should be kept under medical surveillance (if necessary hospitalised) and given rapid and appropriate symptomatic treatment. This may include resumption of Madopar therapy after careful evaluation. Patients should be carefully observed for possible undesirable psychiatric symptoms. Depression may occur during treatment with Madopar, but may also be an effect of the underlying disease. Somnolence and, in rare cases, episodes of sudden sleep onset may occur during treatment with Madopar. Sudden onset of sleep may occur without prior warning signs or previous somnolence and without the patient being aware that the episodes have occurred. Patients must therefore be informed of this risk and warned not to drive or operate machinery if they feel drowsy or have already experienced episodes of sudden sleep onset. A reduction of the dosage or termination of therapy should be considered if the patient experiences somnolence or episodes of sudden sleep onset (see “Effects on ability to drive and use machines”)."	3/11/2022	Roche Ltd
			Warnings related to interactions:	Deletion of text to read " Blood count and liver function should be monitored during the initial treatment phase. Blood sugar levels should be closely monitored in diabetics and antidiabetic dosages adjusted accordingly. Patients with a history of myocardial infarction, coronary heart disease or arrhythmia should undergo regular cardiovascular examination (including, in particular, an ECG). Caution is also mandatory in patients with a history of gastric ulceration or osteomalacia. Madopar must not be abruptly withdrawn since this could cause a life-threatening neuroleptic malignant-like syndrome (hyperpyrexia, muscle rigidity, possible psychological changes and elevated creatine phosphokinase). Should such signs and/or symptoms occur, the patient should be kept under medical surveillance, if necessary in hospital, and given rapid and appropriate symptomatic treatment. This may also include – after careful evaluation of), the situation – the resumption of Madopar therapy. Somnolence and, in rare cases, episodes of sudden sleep onset may occur during treatment with Madopar. Sudden sleep onset may occur without warning signs or previous somnolence and without the patient being aware that the episodes have occurred. Patients must therefore be informed of this risk. They should be advised not to drive or operate machinery if they feel drowsy or have already experienced episodes of sudden sleep onset. Dose reduction or treatment withdrawal should be considered in patients experiencing somnolence or episodes of sudden sleep onset (see Effects on ability to drive and use machines).		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Madopar	Levodopa, benserazide as benserazide hydrochloride.	Pharmacodynamic interactions	Revision of text to read "Combination with anticholinergics, amantadine, selegiline, bromocriptine and dopamine agonists is permissible, though both the desired and the undesired effects of treatment may be intensified. It may be necessary to reduce the dosage of Madopar should not be coadministeredor the other substances. When initiating adjuvant treatment with a COMT inhibitor, a reduction of the dosage of Madopar may be necessary. Experience is available only with tolcapone. It should be noted in particular that anticholinergics must not be withdrawn abruptly when Madopar therapy is instituted, as levodopa does not begin to take effect for some time. General anaesthesia with halothane: Madopar should be discontinued 12-48 hours before surgical interventions requiring general anaesthesia with halothane, as fluctuations in blood pressure and/or arrhythmias may otherwise occur. For general anaesthesia with other anaesthetics see “Warnings and precautions”.	3/11/2022	Roche Ltd
			Effect of other medicinal products on Madopar	Deletion of text to read "Combination with other agents such as anticholinergics, amantadine, selegiline, bromocriptine and dopamine agonists is permissible although this may intensify not only the desirable, but also the undesirable, effects. It may become necessary to reduce the dosage of Madopar or of the other substances. When initiating adjuvant treatment with a COMT inhibitor, it may prove necessary to reduce the dosage of Madopar. Experience in this regard is available only with tolcapone. Particular care must be taken to ensure that anticholinergics are not withdrawn abruptly when starting Madopar therapy as levodopa takes some time to exert its effect.Reduction in the effect of Madopar has been observed after the simultaneous ingestion of a high-protein meal. "under sub tittle other agents/protein rich meals Deletion of text to read "Halothane general anesthesia: Madopar should be discontinued 12–48 hours before surgery under halothane general anesthesia to avoid fluctuations in blood pressure and/or arrhythmias."under sub heading Antipsychotics with dopamine receptor-blocking properties		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Madopar	Levodopa, benserazide as benserazide hydrochloride.	Pregnancy, lactation	Deletion and revision of text under sub heading pregnancy "If a woman becomes pregnant on Madopar therapy, Madopar in the absence of adequate contraception (see “Contraindications). Women of childbearing potential should take a pregnancy test before treatment to exclude pregnancy and should be withdrawn as instructed in Warnings and Precautions. The mode ofuse adequate contraception during treatment with Madopar. If pregnancy occurs in a woman taking Madopar, the drug must be withdrawn, bearing in mind the factors mentioned under “Warnings and precautions”. The manner of withdrawal shouldmust be decided on a case-by-casean individual basis." Revision of text to read under sub heading lactation " The safe use of Madopar during lactation has not been established. Levodopa can inhibit lactation. It is unknownnot known whether benserazide is excretedsecreted in breast milk. Mothers being treated with Madopar shouldmust stop breast-feeding as bonebreastfeeding, since the occurrence of skeletal malformations in their infantsthe infant cannot be excluded."	3/11/2022	Roche Ltd
			Effects on ability to drive and use machines	Revision of text to read "Madopar has a major influence on the ability to drive and use machines."		
			Undesirable effects	Revision of text to read " The frequency categories for undesirable effects are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000), not known (these reactions are reported voluntarily from a population of uncertain size; therefore it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure). The undesirable effects observed in the clinical trials on restless legs syndrome were infrequent and milder than those that occurred with the dosage usually employed in the treatment of Parkinson’s disease."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Madopar	Levodopa, benserazide as benserazide hydrochloride.	Undesirable effects	Revision of text to include sub section undersirable effects after market launch "There have been rare reports of hemolytic anemiahaemolytic anaemia, moderate and transient leukopenia and thrombocytopenia, and a reducedreduction of thromboplastin time. Rises in blood urea nitrogen (BUN) have been observed with Madopar. Therefore, as in any long-term treatment with drugs levodopa-containing levodopa, drugs, the patient's blood count should be checked periodically together with and hepatic and renal function should be regularly monitored." under sub heading class of blood and lymphatic system disorders. Revision of text to read under section undersirable effects after market launch "Uncommon: anorexia. Transient and generally slight rises in transaminasesAnorexia has been observed. Generally mild, transient elevations of transaminase (SGOT, SGPT) and alkaline phosphatase levels have been reported. Increase ofAn increase in gamma-glutamyltransferase has been reported." under sub heading metabolism and nutrition disorders. Revision of text to read under seaction after market launch "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 sub tittle Frequency not known: dopamine dysregulation syndrome. Re vision of text to read under section after market launch " Patients taking Madopar may develop restless legs syndrome. Headaches have been reported. In patients with restless legs syndrome Deterioration (in the sense of shifting the time of symptom occurrence from evening and night to early afternoon and evening) before the next evening dose is the commonest undesirable effect of long-term dopaminergic therapy." Under sub heading Nervous system disorders	3/11/2022	Roche Ltd

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
5	Madopar	Levodopa, benserazide as benserazide hydrochloride.	Properties/Effects	Revision of text to read under sub section mechanism of action "The dopaminergic system is involved in the pathogenesis of restless legs syndrome. Levodopa replacement therapy has therefore been shown to be effective also in patients with restless legs syndrome." Revision of text to read to include under sub section Pharmacodynamics " Madopar LIQ, the tablet for oral suspension, is especially suitable for patients with dysphagia or who require a formulation with a more rapid onset of action, and for parkinsonian patients suffering from early morning or afternoon akinesia or who exhibit “delayed on” or “wearing off” phenomena. The DR tablet is a special formulation that provides biphasic release of the active ingredients in the stomach. The rapid initial release results in rapid achievement of effective plasma levels of levodopa, while the second phase of release ensures that these levels are maintained over several hours. With Madopar DR the concentration peak is considerably reduced as compared with the standard formulations. "	3/11/2022	Roche Ltd
6	Tamoxifen 20 mg film-coated tablets	Tamoxifen	What you need to know before you take Tamoxifen 20 mg film-coated tablets	Revision of text to read under sub title Pregnancy, breastfeeding and fertility "Women of child-bearing age must not become pregnant during treatment with Tamoxifen and for nine months after the end of the treatment. You should therefore use a reliable, non-hormonal contraceptive method (not the ‘pill’, but a hormone-free IUD, condoms or similar) during and for up to nine months after the end of the treatment (see also the section: ‘Taking Tamoxifen with other medicinal products)." Under sub heading Pregnancy	14/11/2022	Novartis
			Tamoxifen 20 mg film-coated tablets contains lactose and sodium	Addition of text to include "and sodium" Under section title Addition of text to read "This medicinal product contains less than 1 mmol (23 mg) sodium per film-coated tablet, this means essentially 'sodium-free'. "		
			Possible side effects	Revision of text to include under sub section Uncommon (may affect up to 1 out of 100 treated persons) " •Reduction in the number of white blood cells (leucopoenia), transient decrease in platelets (thrombocytopoenia), •pneumonia (interstitial pneumonitis). "		
			What Tamoxifen 20 mg film-coated tablets looks like and content of the pack	Revision of text to read "The film-coated tablets are uniform white, round, biconvex, with a score line on one side. The score line is not for dividing the tablet."		