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	Depo-Medrol	Medroxyprogesterone acetate	Special warnings and precautions for use	Addition of text to read under section endocrine effects "Thyrotoxic Periodic Paralysis (TPP) can occur in patients with hyperthyroidism and with methylprednisolone-induced hypokalaemia. TPP must be suspected in patients treated with methylprednisolone presenting signs or symptoms of muscle weakness, especially in patients with hyperthyroidism. If TPP is suspected, levels of blood potassium must be immediately monitored and adequately managed to ensure the restoration of normal levels of blood potassium."	12/05/2025	Pfizer
			Undesirable effects	Addition of ADR under system organ class "Musculoskeletal and connective tissue disorders" to read "post injection pain flare (following intra-articular, periarticular, and tendon sheath injections) under frequency not known. Addition of ADR under system organ class Vascular disorders to read " flushing." under sub section frequency not known.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
2	Depo- Provera	Medroxyprogesterone acetate	What you need to know before you use Depo-Provera	Addition of text under Do not use Depo-Provera to read "• If you have meningioma or have ever been diagnosed with a meningioma (a usually benign tumour of the tissue layer surrounding the brain and spinal cord)." Addition of text Warnings and precautionsn to read Use of medroxyprogesterone acetate has been linked to the development of a usually benign tumour of the tissue surrounding the brain and spinal cord (meningioma). The risk increases especially when you use it for longer duration (several years). If you are diagnosed with meningioma, your doctor will stop your treatment with Depo-Provera (see section 'Do not use Depo-Provera'). If you notice any symptoms such as changes in vision (e.g. seeing double or blurriness), hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, weakness in your arms or legs, you must tell your doctor straightaway."	28/04/2025	Pfizer

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Firialta	10 mg of finerenone	Undesirable effects	Addition of text under system organ class Metabolism and nutrition disorders with frequency commom to read "Hyperuricaemia" Addition of text under sub-section description of selected adverse reactions to read In the pooled data of FIDELIO DKD and FIGARO DKD studies, hyperuricaemia events were reported in 5.1% of finerenone treated patients compared with 3.9% of placebo treated patients. All events were non-serious and did not result in permanent discontinuation in patients who received finerenone. An increase from baseline in mean serum uric acid of 0.3 mg/dL was seen in the finerenone group compared to placebo up to month 16, which attenuated over time. No difference between the finerenone group and the placebo group was observed for reported events of gout (3.0%)." Under title Hyperuricaemia.	19/02/2025	Bayer

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
3	Firialta	10 mg of finerenone	Pharmacodynamic properties	Addition of text under clinical efficacy and safety to read "Patients were required to be receiving standard of care, including a maximum tolerated labelled dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). Patients with diagnosed heart failure with reduced ejection fraction and New York Heart Association II IV were excluded due to the class 1A recommendation for MRA therapy. In the FIDELIO-DKD study patients were eligible based on evidence of persistent albuminuria (> 30 mg/g to 5,000 mg/g), an eGFR of 25 to 75 mL/min/1.73 m2 and serum potassium ≤ 4.8 mmol/L at screening." Addition of text under Clinical studies with no relevant drug drug interactions to read "Multiple doses of 40 mg finerenone once daily had no clinically relevant effect on AUC and C_{max} of the breast cancer resistance protein (BCRP) and organic anion transporting polypeptides (OATP) substrate rosuvastatin.	19/02/2025	Bayer

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Epilim Chrono / Depakine Chrono	Sodium Valprate plus valproic acid	Contraindications	Addition of text to read " Patient with primary, uncorrected, systemic carnitine deficiency (see section 4.4, Patients at risk of hypocarnitinaemia)."	19/03/2025	Sanofi

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Epilim Chrono / Depakine Chrono	Sodium Valprate plus valproic acid	Special warnings	Addition of text to read " • Caution should be exercised in cases of haemorrhagic diathesis. • Sodium valproate has a stimulant effect in vitro on HIV replication in various infected cell lines. Although the clinical significance of these observations is not established, caution should be exercised when administering this substance to patients with AIDS." Revision of text to read under severe hepatic lesions "Experience in epilepsy shows that infants and young children under 3 years of age with severe epilepsy, and especially epilepsy associated with brain lesions, mental retardation and/or congenital metabolic disorders, including mitochondrial disorders, such as carnitine deficiency, urea cycle disorders, POLG mutations (see sections 4.3 and 4.4) or degenerative diseases of genetic origin, are most exposed to this risk, especially in cases of polytherapy. Beyond 3 years of age, the incidence of occurrence decreases significantly and gradually decreases with age. In the vast majority of cases, this hepatic damage has been observed during the first 6 months of treatment."	19/03/2025	Sanofi

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Epilim Chrono / Depakine Chrono	Sodium Valprate plus valproic acid	Special warnings	Revision of text to read under detection "Liver function tests must be performed before starting treatment and then periodically during the first six months of treatment. In the event of changes in concomitant medicinal products (increase in doses or additions) which are known to affect the liver, appropriate liver monitoring must be resumed (see also section 4.5 on the risks of hepatic lesions with salicylates and of other anticonvulsants including cannabidiol). Of the standard examinations, tests reflecting protein synthesis and in particular the PR (prothrombin ratio) are the most relevant." Revision of sub-title to include "• Urea cycle disorders and risk of hyperammonaemia." Addition of text to read under sub-section Patients at risk of hypocarnitinaemia "The administration of valproate may trigger the onset or worsening of hypocarnitinaemia, which may lead to hyperammonaemia (which may itself cause hyperammonaemic encephalopathy).	19/03/2025	Sanofi

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Epilim Chrono / Depakine Chrono	Sodium Valprate plus valproic acid	Special warnings	Other symptoms, such as hepatic toxicity, hypoketotic hypoglycaemia, myopathy (including cardiomyopathy), rhabdomyolysis and Fanconi syndrome, have been observed, mainly in patients with risk factors for hypocarnitinaemia or with pre-existing hypocarnitinaemia. Patients with an increased risk of symptomatic hypocarnitinaemia when treated with valproate are those with metabolic disorders, including carnitine-related mitochondrial disorders (see also section 4.4, Patients with known or suspected mitochondrial illnesses and Urea cycle disorders and risk of hyperammonaemia), patients with impaired carnitine dietary intake, patients under 10 years of age or those using pivalate-conjugated medicinal products or xther antiepileptics concomitantly. Patients should be instructed to immediately report any signs of hyperammonaemia, such as ataxia, disturbances in consciousness or vomiting. Carnitine supplementation must be considered when symptoms of hypocarnitinaemia are observed.	19/03/2025	Sanofi

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Epilim Chrono / Depakine Chrono	Sodium Valprate plus valproic acid	Special warnings	Patients with a primary systemic carnitine deficiency and on treatment for hypocarnitinaemia can only be treated with valproate if the benefits of treatment with valproate outweigh the risks incurred for these patients and in the absence of a therapeutic alternative. In these patients, carnitine monitoring must be implemented. Patients with an underlying carnitine palmitoyltransferase (CPT) II deficiency must be warned about the increased risk of rhabdomyolysis when they take valproate. Carnitine supplementation must be considered in these patients. See also sections 4.5, 4.8, and 4.9."	19/03/2025	Sanofi
			Precautions for use	Revision of text to read under sub-section start and end of treatment "Perform laboratory tests for liver function before starting treatment (see section 4.3, Contraindications), followed by periodic monitoring for the first six months, especially in at-risk patients (see section 4.4, Special warnings). It must be emphasised that, as with most antiepileptics, a moderate, isolated and transient increase in transaminases may be observed, without any clinical signs, especially at the start of treatment. In such cases, it is advisable to perform a more complete laboratory panel (prothrombin ratio, in particular), perhaps reconsider the dosage, and repeat the tests based on the changes in the parameters. It is generally acceptable to suspend treatment if transaminases exceed three times the normal upper limit.		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Epilim Chrono / Depakine Chrono	Sodium Valprate plus valproic acid	Precautions for use	It may be resumed at the minimum effective dosage after normalisation of transaminase levels. If, under these conditions, this level increases again and reaches a value equal to or higher than three times normal, it is recommended that treatment is permanently discontinued. This discontinuation following the increase in transaminases should be done gradually and the dosage should be reduced over one week depending on the size of the daily dose administered. The choice of replacement antiepileptic should be left to the discretion of the doctor depending on the type of epilepsy.”	19/03/2025	Sanofi
			Effects of other medicinal products on valproate	Addition of text to read "An interaction between clonazepam and valproate has been suggested. However, it has not been demonstrated, nor has its mechanism been elucidated. Caution is therefore required in the event of such a combination."		

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Epilim Chrono / Depakine Chrono	Sodium Valprate plus valproic acid	Other interactions	Addition of text under sub-section risk of hepatic lesions "The concomitant use of salicylates must be avoided in children under 3 years of age because of the risk of hepatic toxicity (see section 4.4) The concomitant administration of valproate and several anticonvulsive treatments increases the risk of hepatic lesions, especially in young children (see section 4.4).	19/03/2025	Sanofi

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Epilim Chrono / Depakine Chrono	Sodium Valprate plus valproic acid	Other interactions	Concomitant use with cannabidiol increases the incidence of elevated transaminase enzymes. In clinical trials in patients of any age who were receiving cannabidiol at doses ranging from 10 to 25 mg/kg and valproate at the same time, increases in ALT of more than 3 times the upper limit of normal were reported in 19% of patients. Appropriate liver monitoring must be performed when valproate is used at the same time as other potentially hepatotoxic anticonvulsants, including cannabidiol, and dose reduction or discontinuation should be considered in the event of significant abnormalities in liver parameters (see section 4.4)." Addition of text under Quetiapine to read "The sedative effect of alcohol is increased by valproate." Addition of text under Pivalate-conjugated medicinal products to read "The concomitant administration of valproate and pivalate-conjugated medicinal products (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam, and pivampicillin) must be avoided because of the increased risk of carnitine depletion (see section 4.4, Patients at risk of hypocarnitinaemia). Patients for whom concomitant administration cannot be avoided must be closely monitored to detect any signs or symptoms of hypocarnitinaemia. "	19/03/2025	Sanofi

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
4	Epilim Chrono / Depakine Chrono	Sodium Valprate plus valproic acid	Other interactions	Addition of text under Methotrexate to read "Some reports describe a significant decrease in serum levels of valproate after the administration of methotrexate, with the appearance of convulsions. Prescribers must monitor clinical response (control of fits or mood) and consider monitoring serum levels of valproate, if necessary."	19/03/2025	Sanofi
5	Med rol	Methylprednisolone	4.4. Special warnings and precautions for use	Addition of text under sub-section musculoskeletal to read "Cases of rhabdomyolysis have been reported"	07/02/2025	Pfizer

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
6	Paxlovid	Nirmatrelvir / Ritonvair	Fertility, pregnancy and lactation	Revision of text under Breast-feedng "In a clinical pharmacokinetics study, 8 healthy lactating women who were at least 12 weeks postpartum were administered 3 doses (steady-state dosing) of 300 mg/100 mg nirmatrelvir/ritonavir. Nirmatrelvir and ritonavir were excreted in breastmilk in small amounts, with a milk to plasma AUC ratio of 0.26 and 0.07, respectively. The mean (range) estimated daily infant dose (assuming average milk consumption of 150 mL/kg/day), was 1.8% (1.3-2.5%) and 0.2% (0.1-0.3%) of the maternal dose. There are no available data on the effects of nirmatrelvir or ritonavir on the breast fed newborn/infant or on milk production. A risk to the newborn/infant cannot be excluded. Breast feeding should be discontinued during treatment with Paxlovid and for 48 hours after the last dose of Paxlovid."	28/04/2024	Pfizer
7	Tegretol	200 mg carbamazepine.	CONTRAINDICATIONS	Addition of text to read "•Neonates below 4 weeks of age (see section WARNINGS AND PRECAUTIONS)."	18/02/2025	Novartis

No.	Name of Drug	Active Ingredient(s)	Updated Section	Update	Date of Update	MAH
7	Tegretol	200 mg carbamazepine.	Special excipients	Addiition of text to read "This medicine contains 125 mg propylene glycol in each 5 mL of Tegretol oral suspension which is equivalent to 25 mg per ml. Tegretol oral suspension should not be used in neonates due to known immaturity of both metabolic and renal clearances of propylene glycol in this population: • Term babies (below 4 weeks of age) and • Preterm babies (less than 44 post-menstrual weeks of age) (see section CONTRAINDICATIONS)."	18/02/2025	Novartis