

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1. ELEMENTS FOR SUMMARY TABLES IN THE EPAR

VI.1.1. Summary table of safety concerns

Table 48: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)
	Suicidal Thoughts & behaviour
	Decreased bone density (osteomalacia, osteopenia, osteoporosis and increased risk of fractures)
	Interactions with other products
	Overdose
	Underdose
	Hyperplasia of the gingiva
	Hypersensitivity syndrome (eg DRESS)
	Teratogenicity and Foetal Hydantoin Syndrome
	Hematopoietic events
	Megaloblastic anaemia
	Local and generalized lymphadenopathy, pseudolymphoma, lymphoma
	Cognitive effects
	Dyslipidemia
Important potential risks	Medication errors
	Off-label use
Missing information	None

VI.1.2. Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable

VI.1.3. Summary of Post authorisation efficacy development plan

Not applicable

VI.1.4. Summary table of Risk Minimisation Measures

Table 49: Summary of safety concerns

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Stevens-Johnson Syndrome / Toxic	Appropriate safety labelling	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Epidermal Necrolysis	(SmPC and PIL). Prescription medicine only	
Suicidal Thoughts & behaviour		
Bone Disorders - Osteomalacia		
Interactions with other products		
Overdose		
Underdose		
Hyperplasia of the gingiva		
Hypersensitivity Syndrome (eg DRESS)		
Teratogenicity and Foetal Hydantoin Syndrome		
Hematopoietic events		
Megaloblastic anaemia		
Local and generalized lymphadenopathy, pseudolymphoma, lymphoma		
Cognitive effects		
Dyslipidemia		
Important Potential Risks		
Medication error	Appropriate safety labelling (SmPC and PIL).	None
Off-label use	Prescription medicine only	

VI.2. ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1. Overview of disease epidemiology

Epilepsy is a long-term condition affecting the brain and is characterized by recurring seizures, often accompanied by loss of consciousness. It is one of the most common diseases of the nervous system and approximately 50 million people are currently affected with the disorder worldwide. Epilepsy has no age, sex, race, geography or socio-economy limits. For most patients, there is no identifiable cause. Studies 70% of children and adults suffering from epilepsy can be successfully treated (i.e. their seizures completely controlled) with anti-epileptic drugs (AEDs). (WHO (1))

VI.2.2. Summary of treatment benefits

The studies discussed here below provide reasonable consistent evidence that phenytoin is as effective as other widely used established AEDs in suppressing seizures in common varieties of epilepsy. However, its adverse effect profile, and its lesser ease of use, tend to disadvantage it relative to other agents. (Eadie (74))

- Randomized study with carbamazepine, valproate and phenytoin monotherapy in 181 newly diagnosed patients with generalized or partial seizures, show that all 3 drugs were

highly effective in the control of generalized seizures, but less effective for partial seizures. Callaghan, Kenny (75)

- In a double-blind parallel-groups study with lamotrigine and phenytoin monotherapy in 181 newly diagnosed patients with partial or secondarily or primary generalized tonic-clonic seizures, both drugs were similarly effective against these seizure types. Steiner, Dellaportas (76)
- Cochrane reviews of respectively 551, 661 and 559 subjects with partial seizures, or generalized tonic-clonic seizures with or without other generalized seizure types, suggests no overall difference in effect between nor carbamazepine and phenytoin, nor valproate and phenytoin, nor phenobarbital and phenytoin monotherapy. Additionally, the second review found no statistical difference between treatment with carbamazepine and phenytoin and seizure type (generalized vs partial). The results of the third review favor phenytoin, as phenobarbital was significantly more likely to be withdrawn. Nolan, Marson (77), Taylor, Tudur Smith (78), Tudur Smith, Marson (79), Nolan, Muller (80)

Paediatrics :

- The efficacy and side effects of phenobarbital, phenytoin and sodium valproate in controlling generalized tonic-clonic seizures were compared through a randomized, double blind clinical trial in 151 children aged 4-12 years. The trial concluded that all 3 drugs were equally effective in controlling seizures. Side effects were minimal with sodium valproate followed by phenobarbital . Though side effects were more frequent with phenytoin, most of them disappeared when the drug dosage was adjusted. Thilothammal, Banu (81)
- The effectiveness of clobazam monotherapy was compared to carbamazepine and phenytoin in children aged 2-16 years with partial epilepsies or only generalized tonic-clonic seizures. Seizure control was equivalent for all three medications, as were side effects. Camfield, Booth (82)
- One study concluded that phenobarbital and phenytoin are equally but incompletely effect as anticonvulsants in neonates (Painter, Scher (83)). Another study showed that phenobarbital is more efficacious than phenytoin in the control of clinical seizures in neonates, irrespective of aetiology(Pathak, Upadhyay (84)).

VI.2.3. Unknowns relating to treatment benefits

There are adequate data to support the safety and tolerability of Diphantoïne in different populations and special situations.

VI.2.4. Summary of safety concerns

Important identified risks

Important identified risks are safety issues or undesirable effects for which there is sufficient proof of an association or link with the use of this medicine.

Table 50: information on the important identified risks and their preventability.

Risk	What is known	Preventability
Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis	<p>In very rare cases, a life-threatening skin disorder is reported with the use of Diphantoïne.</p> <p>At first, reddish rounded dots or circular spots, often with blisters in the middle appear on the hull. Additional symptoms such as ulcers in the mouth, throat, nose, genitals and a conjunctivitis (red, swollen eyes) can be seen, as well as flu-like symptoms. The skin rash may evolve into widespread blistering or detachment of the skin. The greatest risk of serious skin reactions occurs within the first weeks of treatment.</p> <p>This risk may be associated with a genetic type in persons of Han Chinese or Thai origin.</p>	<p>If patients experience any of these reactions, they should immediately contact their doctor.</p> <p>In case of the development of these skin disorders, Diphantoïne may never be used again.</p>
Suicidal Thoughts & behaviour	<p>A small number of patients being treated with anti-epileptics have shown a slightly increased risk on suicidal behaviour or thinking. The cause for this is unknown and a causal association with Diphantoïne has not been suggested.</p>	<p>If at any time patients experience suicidal thoughts, they should immediately contact their doctor.</p>
Decreased bone density (osteomalacia, osteopenia, osteoporosis and increase risk of fractures)	<p>Diphantoïne may accelerate the metabolism of vitamin D, which may result in osteomalacia, osteopenia, osteoporosis (weakening of the bones) and increase the risk of fractures.</p>	<p>The use of a vitamin D supplement is recommended.</p>
Interactions with other products	<p>Diphantoïne and certain other medicines may interact with each other.</p> <p>The other medicines may increase or decrease the therapeutic level of the active substance of Diphantoïne and lead to toxicity or</p>	<p>Patients should tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines.</p>

Risk	What is known	Preventability
	<p>in contrary seizures.</p> <p>Diphantoïne may itself also increase or decrease the therapeutic levels of other products.</p>	
Overdose	<p>Diphantoïne has a narrow therapeutic margin and is therefore difficult to dose. If a patient receives a dose higher than appropriate (overdose), this may result in toxicity.</p> <p>A couple of conditions may necessitate a dose lower than normal to obtain the same therapeutic efficacy without toxicity, eg liver or kidney insufficiency.</p>	<p>Patients should let their doctor monitor their blood levels on a regularly basis to make sure the correct dose is administered.</p> <p>Patients should immediately contact their doctor or go to the emergency room in case of signs of overdose (eg gastro-intestinal disorders, trembling eye movements, respiratory problems, uncontrolled movements, trembling, speech disorder, lethargy, hypotension, decreased hearth rate)</p>
Underdose	<p>Diphantoïne has a narrow therapeutic margin and is therefore difficult to dose. If a patient receives a dose lower than appropriate (underdose), this may result in seizures.</p>	<p>Patients should let their doctor monitor their blood levels on a regularly basis to make sure the correct dose is administered.</p> <p>Patients should immediately contact their doctor in case of a higher seizure frequency.</p>
Hyperplasia of the gingiva	<p>Diphantoïne may cause in some patients a swelling of the gums. Gingival hyperplasia occurs more frequently in paediatric patients and in patients with poor oral hygiene</p>	<p>Patients should respect a good dental hygiene and brush their teeth after every meal. A regular check of the appearance of the gums is necessary.</p>
Hypersensitivity syndrome (eg Drug Reaction with Eosinophila and Systemic Symptoms)	<p>In rare cases, patients on Diphantoïne may develop a syndrome with rash, joint pains, eosinophilia (increase in a particular type of white blood cells), fever, liver inflammation, diarrhoea, anorexia, nefritis (inflammation of the kidneys, joined by blood in the urine, fever and pain), anemia, trompocytopenia (less blood</p>	<p>If patients experience any of these reactions, they should contact their doctor immediately.</p>

Risk	What is known	Preventability
	platelets), lymphadenopathy (disorder of the lymph nodes).	
Teratogenicity and Foetal Hydantoin Syndrome	There may be a higher risk on birth defects in babies of epileptic women treated with antiepileptic drugs during pregnancy. When more anti-epileptics including valproate acid are taken at the same time, the risks are probably higher.	Patients should inform their doctor as soon possible about their pregnancy. The doctor will probably adjust the dose of Diphantoïne and prescribe folic acid, vitamin D and K to prevent disorders in the foetus.
Hematopoietic events	There may be an increased risk on disorders of the blood.	Patients should let their doctor monitor their blood values on a regular basis.
Megaloblastic anaemia	Diphantoïne may accelerate the metabolism of folic acid, which may cause megaloblastic anaemia (anemia due to an abnormality in the development of red blood cells).	Patients should let their doctor monitor their blood values on a regular basis. The doctor will probably prescribe folic acid to prevent this disorder.
Local and generalized lymphadenopathy, pseudolymphoma and lymphoma	In rare cases, patients might develop a lymphadenopathy (disease of the lymph nodes) which could result in a malignant lymphoma (tumour).	Patients will be regularly examined by their doctor for signs of lymphadenopathy
Acute hepatotoxicity	Some cases of fatal hepatotoxicity have been reported as part of an hypersensitivity syndrome or alone. Patients who are seriously ill or have liver impairment might be at increased risk for hepatotoxicity.	Patients liver values will be regularly monitored by their doctor.
Cognitive effects	Epilepsy patients have an increased risk for cognitive deficits. Diphantoïne might give an additional risk for cognitive dysfunction.	A slow initial titration, use of lowest dose possible, avoidance of adverse interactions with other medication, use of monotherapy if possible and balance of all these factors with best seizure control.
Dyslipidemia	Patients taking anti-epileptics might be at a higher risk for vascular diseases.	Patients blood lipids will be regular screened and managed if necessary

Important potential risks

Important potential risks are safety issues or undesirable effects for which there is some basis for suspicion of a link with the use of medicine of interest, but this association has not been confirmed.

Table 51: information on the important potential risks identified with the medicinal product.

Risk	What is known (Including reason why it is considered a potential risk)
Medication error	Diphantoïne will be introduced in France. Diphantoïne differs from an established product (Dihydane comprimés sécables containing 100 mg phenytoin base) as regards its strength and pharmaceutical form. Switching from one brand to another might lead to incorrect use and medication errors, that may in some cases result in serious adverse reactions.
Off-label use	Although the risk is considered low, Diphantoïne might be prescribed for another indication than the indications mentioned in the package leaflet. There are many recent studies published in literature in which the active substance of this product is used for other indications.

Missing information

Missing information is information about the safety of a medicine which is not available at the time of submission of a particular risk management plan.

Examples of missing information include populations not studied (e.g. pregnant women or patients with severe renal impairment) or where there is a high likelihood of Off-label use (pill used for indication other than what it is approved for).

There is no missing information.

VI.2.5. Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

These routine risk minimisation activities are considered to be sufficient for each of the safety concerns. This medicine has no additional risk minimisation measures.

VI.2.6. Planned post authorisation development plan

Not applicable. There are no planned post-authorisation studies.

VI.2.7. Summary of changes to the Risk Management Plan over time

Not applicable. This is the first version of the Risk Management Plan for Diphantoïne.