Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pro-Epanutin 75 mg/ml concentrate for solution for infusion/solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fosphenytoin sodium injection is a prodrug intended for parenteral administration; its active metabolite is phenytoin. 1.5 mg of fosphenytoin sodium is equivalent to 1 mg phenytoin sodium, and is referred to as 1 mg phenytoin sodium equivalents (PE). The amount and concentration of fosphenytoin is always expressed in terms of mg PE**.**

One mL of Pro-Epanutin contains 75 mg of fosphenytoin sodium (equivalent to 50 mg of phenytoin sodium) (see section 4.2).

Pro-Epanutin is available in 10 mL and 2 mL vials.

Each 10 mL vial contains 500 mg PE.

Each 2 mL vial contains 100 mg PE.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion/Solution for injection.

Pro-Epanutin is a clear, colourless to pale yellow, sterile solution buffered with trometamol adjusted to pH 8.6 to 9.0 with hydrochloric acid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pro-Epanutin is indicated in adults and children aged 5 years and older:

- for the control of status epilepticus of the tonic-clonic (grand mal) type (see section 4.2).
- for prevention and treatment of seizures occurring in connection with neurosurgery and/or head trauma.
- as substitute for oral phenytoin if oral administration is not possible and/or contra-indicated.

4.2 Posology and method of administration

IMPORTANT NOTE: Throughout all Pro-Epanutin product labelling, the amount and concentration of fosphenytoin is always expressed in terms of phenytoin sodium equivalents (PE) to avoid the need to perform molecular weight-based adjustments when converting between fosphenytoin and phenytoin sodium doses. Pro-Epanutin should always be prescribed and dispensed in phenytoin sodium equivalent units (PE). Note, however, that fosphenytoin has important differences in administration from parenteral phenytoin sodium (see section 4.4).

Phenytoin sodium equivalents (PE):
1.5 mg of fosphenytoin is equivalent to 1 mg phenytoin sodium, and is referred to as 1 mg phenytoin sodium equivalents (PE) (see section 4.4)**.**

Each 10 mL vial of Pro-Epanutin contains 500 mg PE.

Each 2 mL vial of Pro-Epanutin contains 100 mg PE.

Method of administration:

Pro-Epanutin may be administered by intravenous (IV) infusion or by intramuscular (IM) injection. The IM route should be considered for adult patients when there is not an urgent need to control seizures. If rapid phenytoin loading is a primary goal, IV administration of Pro-Epanutin is preferred because the time to achieve therapeutic plasma phenytoin concentrations following IV administration is faster as compared to IM administration.

Pro-Epanutin should not be administered by IM route in emergency situations such as status epilepticus.

Intramuscular (IM) injection is not recommended for children.

Products with particulate matter or discoloration should not be used.

Pro-Epanutin is intended for short-term parenteral administration, and has not been evaluated for periods of more than 5 days.

Posology

Intravenous (IV) infusion
For IV infusion, Pro-Epanutin should be diluted in 5% glucose or 0.9% sodium chloride solution. The concentration should range from 1.5 to 25 mg PE/mL.

Because of the risk of hypotension, the recommended rate of administration by IV infusion in routine clinical settings is 50-100 mg PE/minute. Even in an emergency**, it should not exceed 150 mg PE/minute.** The use of a device controlling the rate of infusion is recommended.

Please refer to tables 1 to 10 for examples of dosing, dilution and infusion time calculations.

Continuous monitoring of electrocardiogram, blood pressure and respiratory function for the duration of the infusion is essential. The patient should also be observed throughout the period where maximal plasma phenytoin concentrations occur. This is approximately 30 minutes after the end of the Pro-Epanutin infusions. Cardiac resuscitative equipment should be available **(see section 4.4)**.

Please refer to Tables 1-10 for examples of dosing, dilution, and infusion time calculations			
Population	**Indication**		**Dosing Table**
Adults	Status epilepticus	Loading dose	Table 1
	Status epilepticus	Maintenance dose	Table 2
	Seizure treatment or prophylaxis	Loading dose	Table 3
	Seizure treatment or prophylaxis	Maintenance dose	Table 4
	Temporary substitution for oral phenytoin		Table 5
Children (aged 5 years and older)	Status epilepticus	Loading dose	Table 6
	Status epilepticus	Maintenance dose	Table 7
	Seizure treatment or prophylaxis	Loading dose	Table 8
	Seizure treatment or prophylaxis	Maintenance dose	Table 9
	Temporary substitution for oral phenytoin		Table 10

DOSAGE IN ADULTS

(For Dose reduction in the Elderly or patients with Renal or Hepatic impairment, please see guidance towards the end of this section.)

Status Epilepticus

Intramuscular (IM) administration of Pro-Epanutin is not recommended in the treatment of status epilepticus.

Loading dose:

In order to obtain rapid seizure control in patients with continuous seizure activity, IV diazepam or lorazepam should be administered prior to administration of Pro-Epanutin.

The loading dose of Pro-Epanutin is 15 mg PE/kg administered as a single dose by IV infusion.

Recommended IV infusion rate (for loading dose in adults):
100 to 150 mg PE/min **(should not exceed 150 mg PE/minute even for emergency use).** See Table 1 for infusion times.

If administration of Pro-Epanutin does not terminate seizures, the use of alternative anticonvulsants should be considered.

Table 1 displays dosing information for status epilepticus loading dose in adults.

TABLE 1 STATUS EPILEPTICUS LOADING DOSE (ADULTS)

Examples of IV loading doses of 15 mg PE[†]/kg, and recommendations for dilution (to 25 mg PE/mL) and IV infusion times (at maximum rate of 150 mg PE/min) by body weight

Weight (Kg)	**Dose (mg PE)**	**Volume of Pro-Epanutin (50 mg PE/mL)**		**Volume (mL) of diluent (5% glucose or 0.9% sodium chloride) for final concentration of 25 mg PE/mL**	**Minimum Infusion Time (minutes) to achieve the maximum recommended infusion rate of 150 mg PE/minute**
		No. of 10 mL vials to open	**Volume (mL) to draw up**		
100	1,500	3	30	30	10
95	1,425	3	28.5	28.5	9.5
90	1,350	3	27	27	9
85	1,275	3	25.5	25.5	8.5
80	1,200	3	24	24	8
75	1,125	3	22.5	22.5	7.5
70	1,050	3	21	21	7
65	975	2	19.5	19.5	6.5
60	900	2	18	18	6
55	825	2	16.5	16.5	5.5
50	750	2	15	15	5
45	675	2	13.5	13.5	4.5

[†]PE - Phenytoin sodium equivalents
Note: Appropriate dose, dosing volume, number of vials of Pro-Epanutin, volume of diluent, and minimum infusion time should always be calculated for the patient's exact body weight when not included in the examples.

Maintenance dose:
The recommended initial maintenance dose of Pro-Epanutin of 4 to 5 mg PE/kg/day may be given as a single dose or in two divided doses, by IV infusion or by IM injection. The initial cumulative daily dose should not exceed 4 to 5 mg PE/kg/day. After administration of a loading dose, maintenance doses should typically be started at the next identified dosing interval. For example, if the intended dose frequency is every 12 hours then the first maintenance dose of Pro-Epanutin should be administered 12 hours after the loading dose.

Maintenance doses should be adjusted according to patient response and trough plasma phenytoin concentrations **(see Therapeutic Drug Monitoring)**.

Recommended IV infusion rate (for maintenance dose in adults):

50 to 100 mg PE/minute **(should not exceed 100 mg PE/minute)**. See Table 2 for infusion times.

Transfer to maintenance therapy with oral phenytoin should be made when appropriate.

Table 2 displays dosing information for status epilepticus maintenance dose in adults.

TABLE 2 STATUS EPILEPTICUS MAINTENANCE DOSE (ADULTS)

Examples for maximum IV maintenance doses of 5 mg PE[†]/kg, recommendations for dilution* (to 25 mg PE/mL or to 1.5 mg PE/mL), and IV infusion times (at maximum rate of 100 mg PE/minute) by body weight

Weight (Kg)	Dose (mg PE)	Volume of Pro-Epanutin (50 mg PE/mL)		Volume (mL) of diluent* (5% glucose or 0.9% sodium chloride)		Minimum Infusion Time (minutes) to achieve the maximum recommended infusion rate of 100 mg PE/minute
		No. of 10 mL vials to open	Volume (mL) to draw up	for final concentration of 25 mg PE/mL	for final concentration of 1.5 mg PE/mL	
100	500	1	10	10	323	5
90	450	1	9	9	291	4.5
80	400	1	8	8	259	4
70	350	1	7	7	226	3.5
60	300	1	6	6	194	3
50	250	1	5	5	162	2.5

*** For IV infusion the final concentration should range between 1.5 and 25 mg PE/mL**
[†]PE - Phenytoin sodium equivalents
Note: Appropriate dose, dosing volume, number of vials of Pro-Epanutin, volume of diluent, and minimum infusion time should always be calculated for the patient's exact body weight when not included in the examples.

Treatment or Prophylaxis of Seizures

Loading dose:
The loading dose of Pro-Epanutin is 10 to 15 mg PE/kg given as a single dose by IV infusion or by IM injection.

Recommended IV infusion rate (for loading dose in adults):
50 to 100 mg PE/minute **(should not exceed 100 mg PE/minute)**. See Table 3 for infusion times.

Table 3 displays dosing information for seizure treatment or prophylaxis loading dose in adults.

TABLE 3 TREATMENT OR PROPHYLAXIS OF SEIZURES LOADING DOSE (ADULTS)

Examples for IV loading doses of 10 mg PE[†]/kg, and recommendations for dilution[a] (to 25 mg PE/mL or to 1.5 mg PE/mL) and IV infusion times (at maximum rate of 100 mg PE/minute) by body weight

Weight (Kg)	Dose (mg PE)	Volume of Pro-Epanutin (50 mg PE/mL)	Volume (mL) of diluent[a] (5% glucose or 0.9% sodium chloride)	Minimum Infusion Time (minutes) to achieve the maximum

		No. of 10mL vials to open	**Volume (mL) to draw up**	**for final concentration of 25 mg PE/mL**	**for final concentration of 1.5 mg PE/mL**	**recommended infusion rate of 100 mg PE/minute**
100	1,000	2	20	20	647	10
90	900	2	18	18	582	9
80	800	2	16	16	517	8
70	700	2	14	14	453	7
60	600	2	12	12	388	6
50	500	1	10	10	323	5

[†]PE - Phenytoin sodium equivalents
[a] For IV infusion the final concentration should range between 1.5 and 25 mg PE/mL
Note: Appropriate dose, dosing volume, number of vials of Pro-Epanutin, volume of diluent, and minimum infusion time should always be calculated for the patient's exact body weight when not included in the examples.

Maintenance dose:
The recommended initial maintenance dose of Pro-Epanutin of 4 to 5 mg PE/kg/day may be given as a single dose or in two divided doses, by IV infusion or by IM injection. The initial cumulative daily dose should not exceed 4 to 5 mg PE/kg/day. After administration of a loading dose, maintenance doses should typically be started at the next identified dosing interval. For example, if the intended dose frequency is every 12 hours then the first maintenance dose of Pro-Epanutin should be administered 12 hours after the loading dose.

Maintenance doses should be adjusted according to patient response and trough plasma phenytoin concentrations **(see Therapeutic Drug Monitoring)**.

Recommended IV infusion rate (for maintenance dose in adults):
50 to 100 mg PE/minute **(should not exceed 100 mg PE/minute)**. See Table 4 for infusion times.

Transfer to maintenance therapy with oral phenytoin should be made when appropriate.

Table 4 displays dosing information for seizure treatment or prophylaxis maintenance dose in adults.

TABLE 4 TREATMENT OR PROPHYLAXIS OF SEIZURES MAINTENANCE DOSE (ADULTS)

Examples for maximum IV maintenance doses of 5 mg PE[†]/kg, recommendations for dilution* (to 25 mg PE/mL or to 1.5 mg PE/mL), and IV infusion times (at maximum infusion rate of 100 mg PE/minute) by body weight

Weight (Kg)	**Dose (mg PE)**	**Volume of Pro-Epanutin (50 mg PE/mL)**		**Volume (mL) of diluent* (5% glucose or 0.9% sodium chloride)**		**Minimum Infusion Time (minutes)**
		No. of 10 mL vials to open	**Volume (mL) to draw up**	**for final concentration of 25 mg PE/mL**	**for final concentration of 1.5 mg PE/mL**	**to achieve the maximum recommended infusion rate of 100 mg PE/minute**
100	500	1	10	10	323	5

90	450	1	9	9	291	4.5
80	400	1	8	8	259	4
70	350	1	7	7	226	3.5
60	300	1	6	6	194	3
50	250	1	5	5	162	2.5

***For IV infusion the final concentration should range between 1.5 and 25 mg PE/mL**
†PE - Phenytoin sodium equivalents
Note: Appropriate dose, dosing volume, number of vials of Pro-Epanutin, volume of diluent, and minimum infusion time should always be calculated for the patient's exact body weight when not included in the examples.

Temporary substitution of oral phenytoin sodium therapy with Pro-Epanutin

The same total daily phenytoin sodium equivalents (PE) dose and dosing frequency as for oral phenytoin sodium therapy should be used and can be administered by IV infusion or by IM injection.

Therapeutic drug monitoring may be useful whenever switching between products and/or routes of administration. Doses should be adjusted according to patient response and trough plasma phenytoin concentrations (see **Therapeutic Drug Monitoring**).

Recommended IV infusion rate (for temporary substitution dose in adults):
50 to 100 mg PE/minute **(should not exceed 100 mg PE/minute)**. See Table 5 for infusion times.

Table 5 displays dosing information for the temporary substitution of oral phenytoin sodium in adults.

TABLE 5 TEMPORARY SUBSTITUTION FOR ORAL PHENYTOIN SODIUM THERAPY (ADULTS)

Examples of equivalent doses and recommendations for dilution* (to 25 mg PE†/mL or to 1.5 mg PE/mL), and IV infusion times (at maximum rate of 100 mg PE/minute)

Dose (mg phenytoin sodium)	Dose (mg PE)	Volume of Pro-Epanutin (50 mg PE/mL)		Volume (mL) of diluent* (5% glucose or 0.9% sodium chloride)		Minimum Infusion Time (minutes) to achieve the maximum recommended infusion rate of 100 mg PE/minute
		No. of 10 mL vials to open	Volume (mL) to draw up	for final concentration of 25 mg PE/mL	for final concentration of 1.5 mg PE/mL	
500	500	1	10	10	323	5
450	450	1	9	9	291	4.5
400	400	1	8	8	259	4
350	350	1	7	7	226	3.5
300	300	1	6	6	194	3
250	250	1	5	5	162	2.5

*** For IV infusion the final concentration should range between 1.5 and 25 mg PE/mL**
†PE - Phenytoin sodium equivalents
Note: Appropriate dose, dosing volume, number of vials of Pro-Epanutin, volume of diluent, and minimum infusion time should always be calculated for the patient's exact body weight when not included in the examples.

DOSAGE IN CHILDREN

Neonates and children aged up to 5 years
The safety and efficacy of Pro-Epanutin in children under 5 years has not been established.

Children aged 5 years and older
Pro-Epanutin may be administered to children (ages 5 years and older) by IV infusion only, at the same mg PE/kg dose used for adults. The doses of Pro-Epanutin for children have been predicted from the known pharmacokinetics of Pro-Epanutin in adults and children aged 5 to 10 years and of parenteral phenytoin in adults and children.

Intramuscular (IM) administration in children is not recommended.

For Dose reduction in patients with Renal or Hepatic impairment, please see guidance towards the end of this section.

Status Epilepticus

Loading dose:
In order to obtain rapid seizure control in patients with continuous seizure activity IV diazepam or lorazepam should be administered prior to administration of Pro-Epanutin.

The loading dose of Pro-Epanutin is 15 mg PE/kg administered as a single dose by IV infusion.

Recommended IV infusion rate (for loading dose in children):
2 to 3 mg PE/kg/min **(should not exceed 3 mg PE/kg/minute or 150 mg PE/minute, whichever is slower).** See Table 6 for infusion times.

If administration of Pro-Epanutin does not terminate seizures, the use of alternative anticonvulsants should be considered.

Table 6 displays dosing information for status epilepticus loading dose in children.

TABLE 6 STATUS EPILEPTICUS LOADING DOSE (CHILDREN AGED 5 YEARS AND OLDER)

Examples of IV loading doses of 15 mg PE[†]/kg and recommendations for dilution (to 25 mg PE/mL) and IV infusion times (at maximum rate of 3 mg PE/kg/minute) by body weight

Weight (Kg)	**Dose (mg PE)**	**Volume of Pro-Epanutin (50 mg PE/mL)**		**Volume (mL) of diluent (5% glucose or 0.9% sodium chloride) for final concentration of 25 mg PE/mL**	**Minimum Infusion Time (minutes) to achieve the maximum recommended infusion rate of 3 mg PE/kg/minute**
		No. of 10 mL vials to open	**Volume (mL) to draw up**		
47.5	712.5	2	14.25	14.25	5
45	675	2	13.5	13.5	5
42.5	637.5	2	12.75	12.75	5
40	600	2	12	12	5
37.5	562.5	2	11.25	11.25	5
35	525	2	10.5	10.5	5
32.5	487.5	1	9.75	9.75	5
30	450	1	9	9	5
27.5	412.5	1	8.25	8.25	5
25	375	1	7.5	7.5	5

22.5	337.5	1	6.75	6.75	5
20	300	1	6	6	5
17.5	262.5	1	5.25	5.25	5

[†]PE - Phenytoin sodium equivalents
Note: Appropriate dose, dosing volume, number of vials of Pro-Epanutin, volume of diluent, and minimum infusion time should always be calculated for the patient's exact body weight when not included in the examples.

Maintenance dose:
The recommended initial maintenance dose of Pro-Epanutin of 4 to 5 mg PE/kg/day may be given as a single dose or in up to four divided doses, by IV infusion. The initial cumulative daily dose should not exceed 4 to 5 mg PE/kg/day. After administration of a loading dose, maintenance doses should typically be started at the next identified dosing interval. For example, if the intended dose frequency is every 12 hours then the first maintenance dose of Pro-Epanutin should be administered 12 hours after the loading dose.

Maintenance doses should be adjusted according to patient response and trough plasma phenytoin concentrations **(see Therapeutic Drug Monitoring).**

Recommended IV infusion rate (for maintenance dose in children):
1 to 2 mg PE/kg/minute **(should not exceed 2 mg PE/kg/minute or 100 mg PE/minute whichever is slower).** See Table 7 for infusion times.

Transfer to maintenance therapy with oral phenytoin should be made when appropriate.

Table 7 displays dosing information for status epilepticus maintenance dose in children.

TABLE 7 STATUS EPILEPTICUS MAINTENANCE DOSE (CHILDREN AGED 5 YEARS AND OLDER)

Examples for maximum IV maintenance doses of 5 mg PE[†]/kg, recommendations for dilution* (to 25 mg PE/mL or to 1.5 mg PE/mL) and IV infusion times (at maximum rate of 2 mg PE/kg/minute) by body weight

Weight (Kg)	Dose (mg PE)	Volume of Pro-Epanutin (50 mg PE/mL)		Volume (mL) of diluent (5% glucose or 0.9% sodium chloride)		Minimum Infusion Time (minutes) to achieve the maximum recommended infusion rate of 2 mg PE/kg/minute
		No. of 10 mL vials to open	Volume (mL) to draw up	for final concentration of 25 mg PE/mL	for final concentration of 1.5 mg PE/mL	
47.5	237.5	1	4.75	4.75	154	2.5
45	225	1	4.5	4.5	146	2.5
42.5	212.5	1	4.25	4.25	137	2.5
40	200	1	4	4	129	2.5
37.5	187.5	1	3.75	3.75	121	2.5
35	175	1	3.5	3.5	113	2.5
32.5	162.5	1	3.25	3.25	105	2.5
30	150	1	3	3	97	2.5
27.5	137.5	1	2.75	2.75	89	2.5
25	125	1	2.5	2.5	81	2.5
22.5	112.5	1	2.25	2.25	73	2.5
20	100	1	2	2	65	2.5
17.5	87.5	1	1.75	1.75	57	2.5

*** For IV infusion the final concentration should range between 1.5 and 25 mg PE/mL**
†PE - Phenytoin sodium equivalents
Note: Appropriate dose, dosing volume, number of vials of Pro-Epanutin, volume of diluent, and minimum infusion time should always be calculated for the patient's exact body weight when not included in the examples.

Treatment or Prophylaxis of Seizures

Loading dose:

The loading dose of Pro-Epanutin is 10 to 15 mg PE/kg given as a single dose by IV infusion.

Recommended IV infusion rate (for loading dose in children):
1 to 2 mg PE/kg/minute **(should not exceed 2 mg PE/kg/minute or 100 mg PE/minute, whichever is slower).** See Table 8 for infusion times.

Table 8 displays dosing information for seizure treatment or prophylaxis loading dose in children.

TABLE 8 TREATMENT OR PROPHYLAXIS OF SEIZURES LOADING DOSE (CHILDREN AGED 5 YEARS AND OLDER)

Examples for IV loading doses of 10 mg PE† /kg, and recommendations for dilution[a] (to 25 mg PE/mL or to 1.5 mg PE/mL) and IV infusion times (at maximum rate of 2 mg PE/kg/minute) by body weight

Weight (Kg)	Dose (mg PE)	Volume of Pro-Epanutin (50 mg PE/mL)		Volume (mL) of diluent[a] (5% glucose or 0.9% sodium chloride)		Minimum Infusion Time (minutes) to achieve the maximum recommended infusion rate of 2 mg PE /kg/ minute
		No. of 10 mL vials to open	Volume (mL) to draw up	for final concentration of 25 mg PE/mL	for final concentration of 1.5 mg PE/mL	
47.5	475	1	9.5	9.5	307	5
45	450	1	9	9	291	5
42.5	425	1	8.5	8.5	275	5
40	400	1	8	8	259	5
37.5	375	1	7.5	7.5	243	5
35	350	1	7	7	226	5
32.5	325	1	6.5	6.5	210	5
30	300	1	6	6	194	5
27.5	275	1	5.5	5.5	178	5
25	250	1	5	5	161	5
22.5	225	1	4.5	4.5	145	5
20	200	1	4	4	129	5
17.5	175	1	3.5	3.5	113	5

†PE - Phenytoin sodium equivalents
[a] For IV infusion the final concentration should range between 1.5 and 25 mg PE/mL
Note: Appropriate dose, dosing volume, number of vials of Pro-Epanutin, volume of diluent, and minimum infusion time should always be calculated for the patient's exact body weight when not included in the examples.

Maintenance dose:

The recommended initial maintenance dose of Pro-Epanutin of 4 to 5 mg PE/kg/**day** may be given as a single dose or in up to four divided doses, by IV infusion. The initial cumulative daily dose should not exceed 4 to 5 mg PE/kg/day. After administration of a loading dose, maintenance doses should typically be started at the next identified dosing interval. For example, if the intended dose frequency is every 12 hours then the first maintenance dose of Pro-Epanutin should be administered 12 hours after the loading dose.

Maintenance doses should be adjusted according to patient response and trough plasma phenytoin concentrations **(see Therapeutic Drug Monitoring).**

Recommended IV infusion rate (for maintenance dose in children):
1 to 2 mg PE/kg/minute **(should not exceed 2 mg PE/kg/minute or 100 mg PE/minute, whichever is slower).** See Table 9 for infusion times.

Transfer to maintenance therapy with oral phenytoin should be made when appropriate.

Table 9 displays dosing information for seizure treatment or prophylaxis maintenance dose in children.

TABLE 9 TREATMENT OR PROPHYLAXIS OF SEIZURES MAINTENANCE DOSE (CHILDREN AGED 5 YEARS AND OLDER)

Examples for maximum IV maintenance doses of 5 mg PE[†]/kg, recommendations for dilution* (to 25 mg PE/mL or to 1.5 mg PE/kg), and IV infusion times (at a maximum rate of 2 mg PE/kg/minute) by body weight

Weight (Kg)	Dose (mg PE)	Volume of Pro-Epanutin (50 mg PE/mL)		Volume (mL) of diluent (5% glucose or 0.9% sodium chloride)		Minimum Infusion Time (minutes) to achieve the maximum recommended infusion rate of 2 mg PE/kg/ minute
		No. of 10 mL vials to open	Volume (mL) to draw up	for final concentration of 25 mg PE/mL	for final concentration of 1.5 mg PE/mL	
47.5	237.5	1	4.75	4.75	154	2.5
45	225	1	4.50	4.50	146	2.5
42.5	212.5	1	4.25	4.25	137	2.5
40	200	1	4	4	129	2.5
37.5	187.5	1	3.75	3.75	121	2.5
35	175	1	3.5	3.5	113	2.5
32.5	162.5	1	3.25	3.25	105	2.5
30	150	1	3	3	97	2.5
27.5	137.5	1	2.75	2.75	89	2.5
25	125	1	2.5	2.5	81	2.5
22.5	112.5	1	2.25	2.25	73	2.5
20	100	1	2	2	65	2.5
17.5	87.5	1	1.75	1.75	57	2.5

*** For IV infusion the final concentration should range between 1.5 and 25 mg PE/mL**
[†]PE - Phenytoin sodium equivalents
Note: Appropriate dose, dosing volume, number of vials of Pro-Epanutin, volume of diluent, and minimum infusion time should always be calculated for the patient's exact body weight when not included in the examples.

Temporary substitution of oral phenytoin sodium therapy with Pro-Epanutin

The same total daily phenytoin sodium equivalents (PE) dose and dosing frequency as for oral phenytoin sodium therapy should be administered by IV infusion.

Therapeutic drug monitoring may be useful whenever switching between products and/or routes of administration Doses should be adjusted according to patient response and trough plasma phenytoin concentrations **(see Therapeutic Drug Monitoring).**

Recommended IV infusion rate (for temporary substitution dose in children):
1 to 2 mg PE/kg/minute **(should not exceed 2 mg PE/kg/minute or 100 mg PE/minute, whichever is slower).** See Table 10 for infusion times.

Table 10 displays dosing information for the temporary substitution of oral phenytoin sodium in children.

TABLE 10 TEMPORARY SUBSTITUTION FOR ORAL PHENYTOIN SODIUM THERAPY (CHILDREN AGED 5 YEARS AND OLDER)

Examples of equivalent doses and recommendations for dilution* (to 25 mg PE[†]/mL or to 1.5 mg PE/mL), and IV infusion times (at maximum rate of 2 mg PE/kg/minute)

Dose (mg phenytoin sodium) **5 mg/kg**	**Dose (mg PE)**	**Volume of Pro-Epanutin (50 mg PE/mL)**		**Volume (mL) of diluent* (5% glucose or 0.9% sodium chloride)**		**Minimum Infusion Time (minutes)** **to achieve the maximum recommended infusion rate of 2 mg PE/kg/minute**
		No. of 10mL vials to open	**Volume (mL) to draw up**	**for final concentration of 25 mg PE/mL**	**for final concentration of 1.5 mg PE/mL**	
175	175	1	3.5	3.5	113	2.5
150	150	1	3	3	97	2.5
125	125	1	2.5	2.5	81	2.5
100	100	1	2	2	65	2.5
75	75	1	1.5	1.5	49	2.5
50	50	1	1	1	32	2.5

*** For IV infusion the final concentration should range between 1.5 and 25 mg PE/mL**
[†]PE - Phenytoin sodium equivalents

Elderly patients
A lower loading dose and/or infusion rate, and lower or less frequent maintenance dosing of Pro-Epanutin may be required. Phenytoin metabolism is slightly decreased in elderly patients. A 10% to 25% reduction in dose or rate may be considered and careful clinical monitoring is required.

Patients with renal or hepatic disease
Except in the treatment of status epilepticus, a lower loading dose and/or infusion rate, and lower or less frequent maintenance dosing may be required in patients with renal and/or hepatic disease or in those with hypoalbuminaemia. A 10% to 25% reduction in dose or rate may be considered and careful clinical monitoring is required.

The rate of conversion of IV Pro-Epanutin to phenytoin may be increased in these patients. While the clearance rate of total phenytoin is not affected, the plasma unbound phenytoin concentrations may be elevated. Unbound concentration of phenytoin may be elevated in patients with hyperbilirubinaemia (see section 4.4). It is therefore more appropriate to measure plasma unbound phenytoin concentrations rather than plasma total phenytoin concentrations in these patients (see section 5.2).

Therapeutic drug monitoring
Prior to complete conversion, immunoanalytical techniques may significantly overestimate plasma phenytoin concentrations due to cross-reactivity with fosphenytoin. Chromatographic assay methods (e.g. HPLC) accurately quantitate phenytoin concentrations in biological fluids in the presence of fosphenytoin. It is advised that blood samples to assess phenytoin concentration ***should not*** be obtained for at least 2 hours after IV Pro-Epanutin infusion or 4 hours after IM Pro-Epanutin injection.

Optimal seizure control without clinical signs of toxicity occurs most often with plasma total phenytoin concentrations of between 10 and 20 mg/l (40 and 80 micromoles/l) or plasma unbound phenytoin concentrations of between 1 and 2 mg/l (4 and 8 micromoles/l).

Plasma phenytoin concentrations sustained above the optimal range may produce signs of acute toxicity **(see section 4.4)**.

Phenytoin capsules are approximately 90% bioavailable by the oral route. Phenytoin, supplied as Pro-Epanutin, is 100% bioavailable by both the IM and IV routes. For this reason, plasma phenytoin concentrations may increase when IM or IV Pro-Epanutin is substituted for oral phenytoin sodium therapy. However, it is not necessary to adjust the initial doses when substituting oral phenytoin with Pro-Epanutin or vice versa.

Therapeutic drug monitoring may be useful whenever switching between products and/or routes of administration.

4.3 Contraindications

Hypersensitivity to fosphenytoin sodium, phenytoin or other hydantoins, or to any of the excipients listed in section 6.1.

Parenteral phenytoin affects ventricular automaticity. Pro-Epanutin is therefore, contra-indicated in patients with sinus bradycardia, sino-atrial block, second and third degree A-V block and Adams-Stokes syndrome.

Acute intermittent porphyria.

Coadministration of Pro-Epanutin is contra-indicated with delavirdine due to the potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Phenytoin sodium equivalents (PE)

Pro-Epanutin is a prodrug intended for parenteral administration; its active metabolite is phenytoin. 1.5 mg of fosphenytoin sodium is equivalent to 1 mg phenytoin sodium, and is referred to as 1 mg phenytoin sodium equivalents (PE). The amount and concentration of fosphenytoin is always expressed in terms of mg PE.

Intravenous (IV) Infusion rate

Adults:
Pro-Epanutin should be administered IV at a rate no greater than 150 mg PE/min due to the risk of cardiovascular toxicity (see section 4.2).

Children (5 years and older):
Pro-Epanutin should be administered at a rate no greater than 3 mg PE/kg/min or 150 mg PE/min, whichever is slower, due to the risk of cardiovascular toxicity (see section 4.2).

Note that Pro-Epanutin has important differences in administration from parenteral phenytoin sodium.

Dosing Errors
Dosing errors associated with Pro-Epanutinhave resulted in patients receiving the wrong dose of Pro-Epanutin. Pro-Epanutin is marketed in 2 mL and 10 mL vials at a concentration of 50 mg PE/mL. A 2 mL vial contains a total of 100 mg PE and a 10 mL vial contains a total of 500 mg PE. Errors have occurred when the concentration of the vial (50 mg PE/mL) was misinterpreted to mean that the total content of the vial was 50 mg PE, resulting in two- or ten-fold overdoses of Pro-Epanutin .

There have been other causes of dosing errors, including product name confusion, product preparation errors, drug infusion/administration errors and incorrect dose calculations. In some cases, overdoses were associated with fatal outcomes, including in children under 5 years of age.

To help minimize confusion, the prescribed dose of Pro-Epanutin should always be expressed in milligrams of phenytoin equivalents (mg PE) (see section 4.2). Care should be taken to ensure the appropriate volume of Pro-Epanutin is withdrawn from the vial when preparing the drug for administration. Attention to these details may prevent some Pro-Epanutin medication errors from occurring.

Monitoring of Patients
Continuous monitoring of electrocardiogram, blood pressure and respiratory function for the duration of the infusion is essential. The patient should also be observed throughout the period where maximal plasma phenytoin concentrations occur. This is approximately 30 minutes after the end of the Pro-Epanutin infusions. Cardiac resuscitative equipment should be available.

Cardiovascular Effect
Pro-Epanutin should be used with caution in patients with hypotension and severe myocardial insufficiency. Severe cardiovascular reactions including atrial and ventricular conduction depression, ventricular fibrillation, asystole and fatalities have been reported following phenytoin and fosphenytoin administration. Hypotension may also occur following IV administration of high doses and/or high infusion rates of Pro-Epanutin and even within recommended doses and rates. A reduction in the rate of administration or discontinuation of dosing may be necessary (see section 4.2).

Severe cardiac complications have been reported in elderly, children (especially infants), or gravely ill patients following administration of fosphenytoin. Cardiac adverse events have also been reported in adults and children without underlying cardiac disease or comorbidities and at recommended doses and infusion rates. Therefore, careful cardiac (including respiratory) monitoring is needed when administering IV loading doses of fosphenytoin.

Patients with an acute cerebrovascular event may be at increased risk of hypotension and require particularly close monitoring.

Absence Seizures
Phenytoin is not effective in absence seizures. If tonic-clonic seizures are present simultaneously with absence seizures, combined drug therapy is recommended.

Withdrawal Precipitated Seizure/Status Epilepticus
Abrupt withdrawal of antiepileptic drugs may increase seizure frequency and may lead to status epilepticus.

Suicidal Ideation and Behaviour
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised, placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for fosphenytoin.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Local Toxicity (including Purple Glove Syndrome)
Edema, discoloration, and pain distal to the site of injection (described as "purple glove syndrome") have also been reported following peripheral IV fosphenytoin injection. This may or may not be associated with extravasation. The syndrome may not develop for several days after injection. Although resolution of symptoms may occur without treatment, skin necrosis and limb ischemia have occurred that required surgical interventions and, in rare cases, amputation.

Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms (HSS/DRESS)
Hypersensitivity Syndrome (HSS) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking anticonvulsant drugs, including phenytoin and fosphenytoin. Some of these events have been fatal or life threatening.

HSS/DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leukocytosis, and eosinophilia. The interval between first drug exposure and symptoms is usually 2-4 weeks of treatment but has also been reported in individuals receiving anticonvulsants for 3 or more months. If such signs and symptoms occur, the patient should be evaluated immediately. Fosphenytoin should be discontinued if an alternative etiology for the signs and symptoms cannot be established.

Patients at higher risk for developing HSS/DRESS include black patients, patients who have experienced this syndrome in the past (with phenytoin, fosphenytoin or other anticonvulsant drugs), patients who have a family history of this syndrome and immuno-suppressed patients. The syndrome is more severe in previously sensitized individuals.

Serious Cutaneous Adverse Reactions

Fosphenytoin can cause severe cutaneous adverse reactions (SCARs) such as acute generalized exanthematous pustulosis (AGEP) exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS, which can be fatal. Although serious skin reactions may occur without warning, patients should be alert for the occurrence of rash and other symptoms of HSS/DRESS and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. The physician should advise the patient to discontinue treatment if the rash appears. If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further fosphenytoin or phenytoin administration is contraindicated.

The risk of serious skin reactions and other hypersensitivity reactions to phenytoin may be higher in black patients.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking drugs associated with SJS/TEN, including phenytoin. Case-control, genome-wide association studies in Taiwanese, Japanese, Malaysian and Thai patients have identified an increased risk of SCARs in carriers of the decreased function CYP2C9*3 variant.

Literature reports suggest that the combination of phenytoin, cranial irradiation and the gradual reduction of corticosteroids may be associated with the development of erythema multiforme, and/or Stevens-Johnson syndrome, and/or toxic epidermal necrolysis.

Drug rash with eosinophilia and systemic symptoms (DRESS) reflects a serious hypersensitivity reaction to drugs, characterized by skin rash, fever, lymph node enlargement, and internal organ involvement. Cases of DRESS have been noted in patients taking phenytoin.

CYP2C9 metabolism

Phenytoin is metabolised by the CYP450 CYP2C9 enzyme. Patients who are carriers of the decreased function CYP2C9*2 or CYP2C9*3 variants (intermediate or poor metabolisers of CYP2C9 substrates) may be at risk of increased phenytoin plasma concentrations and subsequent toxicity. In patients who are known to be carriers of the decreased function CYP2C9*2 or *3 alleles, close monitoring of clinical response is advised and monitoring of plasma phenytoin concentrations may be required.

Angioedema

Angioedema has been reported in patients treated with phenytoin and fosphenytoin. Eosphenytoin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

Hepatic Injury

The liver is the chief site of biotransformation of phenytoin.
Toxic hepatitis and liver damage have been reported with phenytoin and may, in rare cases, be fatal.
Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents usually occur within the first 2 months of treatment and may be associated with HSS/DRESS. Patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.
The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In patients with acute hepatotoxicity, fosphenytoin should be immediately discontinued and not re-administered.
The risk of hepatotoxicity and other hypersensitivity reactions to phenytoin may be higher in black patients.

Haematopoietic System

Haematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression (see section 4.8).

Lymphadenopathy (local or generalised) including benign lymph node hyperplasia, pseudolymphoma, lymphoma and Hodgkin's Disease have been associated with administration of phenytoin, although a cause and effect relationship has not been established. It is therefore, important to eliminate other types of lymph node pathology before discontinuing therapy with Pro-Epanutin. Lymph node involvement may occur with or without symptoms and signs resembling HSS/DRESS described above. In all cases of lymphadenopathy, long term follow-up observations are indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute Toxicity

Confusional states referred to as "delirium", "psychosis" or "encephalopathy" or rarely irreversible cerebellar dysfunction and/or cerebellar atrophy may occur if plasma phenytoin concentrations are sustained above the optimal therapeutic range and/or long-term phenytoin use. Plasma phenytoin concentrations should be determined at the first sign of acute toxicity (see Section 4.2). If plasma phenytoin concentrations are excessive, the dose of Pro-Epanutin should be reduced. If symptoms persist, administration of Pro-Epanutin should be discontinued.

Renal or Hepatic Disease

Pro-Epanutin should be used with caution in patients with renal and/or hepatic disease, or in those with hypoalbuminaemia.

Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminaemia, the interpretation of total phenytoin plasma concentrations should be made with caution as it may not reflect the pharmacologically active unbound concentration. Unbound concentration of phenytoin may be elevated in patients with hyperbilirubinaemia. Unbound phenytoin concentrations are more appropriate in these patients (see sections 4.2 and 5.2). Alterations in dosing may be necessary in patients with impaired kidney or liver function, elderly patients or those who are gravely ill (see Section 4.2). These patients may show early signs of phenytoin toxicity or an increase in the severity of adverse events due to alterations in Pro-Epanutin and phenytoin pharmacokinetics.

The phosphate load provided by Pro-Epanutin is 0.0037 mmol phosphate/mg fosphenytoin sodium. Caution is advised when administering Pro-Epanutin in patients requiring phosphate restriction, such as those with severe renal impairment.

Sensory Disturbances

Overall these occur in 13% of the patients exposed to Pro-Epanutin. Transient itching, burning, warmth or tingling in the groin during and shortly after IV infusion of Pro-Epanutin may occur. The sensations are not consistent with the signs of an allergic reaction and may be avoided or minimised by using a slower rate of IV infusion or by temporarily stopping the infusion.

Diabetes

Phenytoin may raise blood glucose in diabetic patients.

Alcohol Use

Acute alcohol intake may increase plasma phenytoin concentrations while chronic alcohol use may decrease plasma phenytoin concentrations.

Women of Childbearing Potential

Pro-Epanutin may cause foetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse development outcomes (see section 4.6).

Sodium Content

When calculating the total amount of sodium, any dilution of fosphenytoin sodium injection with sodium chloride solution should be taken into consideration (see section 6.6).

Fosphenytoin sodium injection 75 mg/mL contains 8.5 mg sodium per mL.

Pro-Epanutin is available in 10 mL and 2 mL vials.

Each 10 mL vial contains 85 mg sodium equivalent to 4.25% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Each 2 mL vial contains 17 mg sodium equivalent to 0.85% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions which may occur following the administration of Pro-Epanutin are those that are expected to occur with drugs known to interact with phenytoin. Phenytoin metabolism is saturable and other drugs that utilise the same metabolic pathways may alter plasma phenytoin concentrations. There are many drugs which may increase or decrease plasma phenytoin concentrations. Equally phenytoin may affect the metabolism of a number of other drugs because of its potent enzyme-inducing potential. Determination of plasma phenytoin concentrations is especially helpful when possible drug interactions are suspected (see section 4.2).

No drugs are known to interfere with the conversion of fosphenytoin to phenytoin.

Phenytoin is extensively bound to plasma proteins and is prone to competitive displacement. Drugs highly bound to albumin could also increase the fosphenytoin unbound fraction with the potential to increase the rate of conversion of fosphenytoin to phenytoin.

Phenytoin is mainly metabolized in the liver by the cytochrome P450 CYP2C9 and CYP2C19 enzymes.

Inhibition of phenytoin metabolism may produce significant increases in plasma phenytoin concentrations and increase the risk of phenytoin toxicity. Phenytoin is also a potent inducer of hepatic drug-metabolising enzymes and may reduce the levels of drugs metabolized by these enzymes.

The following drug interactions are the most commonly occurring drug interactions with phenytoin:
Drugs that may increase serum phenytoin concentrations listed by likely mechanism:

Drug[a]	Mechanism
Antineoplastic agents (fluorouracil) Azole antifungals (ketoconazole, itraconazole, fluconazole, miconazole) Capecitabine Fluvastatin Glibenclamide Sulfaphenazole	CYP2C9 inhibition
Felbamate Oxcarbazepine Topiramate	CYP2C19 inhibition
Azapropazone Fluvoxamine Nifedipine Sertraline Ticlopidine Tolbutamide Voriconazole	CYP2C9/2C19 inhibition
Acute alcohol intake Amiodarone Amphotericin B Chloramphenicol Diltiazem (high doses) Disulfiram Fluoxetine H2-antagonists (cimetidine) Halothane Isoniazid Methylphenidate	Unknown mechanism

Oestrogens Omeprazole Phenothiazines Phenylbutazone Salicylates Sodium valproate Succinimides (ethosuximide) Sulfonamides (sulfadiazine, sulfamethizole, sulfamethoxazole-trimethoprim) Tacrolimus Trazodone Viloxazine	
[a] The list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted.	

Drugs that may decrease plasma phenytoin concentrations listed by likely mechanism:

Drug[a]	Mechanism
Rifampicin	CYP2C/2C19 induction
Antineoplastic agents (bleomycin, carboplatin, cisplatin, doxorubicin, methotrexate) Chronic alcohol abuse Diazoxide Folic acid Fosamprenavir Nelfinavir[b] Theophylline Vigabatrin Ritonavir St John's Wort	Unknown
[a] This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted. [b] Co-administration of nelfinavir tablets (1,250 mg twice a day) with phenytoin capsules (300 mg once a day) did not change the plasma concentration of nelfinavir. However, co-administration of nelfinavir reduced the AUC values of phenytoin (total) and free phenytoin by 29% and 28%, respectively. Plasma concentrations of phenytoin should be monitored during concomitant treatment with nelfinavir.	

Drugs that may increase or decrease phenytoin concentrations listed by likely mechanism:

Drug[a]	Mechanism
Antineoplastic agents Carbamazepine Chlordiazepoxide Ciprofloxacin Diazepam Phenobarbital Phenothiazines Sodium valproate [b] Valproic acid [b] Certain antacids	Unknown
[a] This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted. [b] Sodium valproate and valproic acid are similar medications. The term valproate has been used to represent these medications.	

Drugs whose serum levels and/or effects may be altered by phenytoin listed by likely mechanism:

Drug[a]	Mechanism
Antineoplastic agents (e.g. Teniposide) Atorvastatin Carbamezepine Ciclosporin Disopyramide Efavirenz	CYP3A4 induction

Erythromycin Fosamprenavir Indinavir Lopinavir/ritonavir Methadone Nelfinavir Neuromuscular blocking agents (pancuronium, vecuronium) Nicardipine Nifedipine Nisoldipine Praziquantel Ritonavir Saquinavir Simvastatin Verapamil	
Chlorpropamide Fluvastatin	CYP2C9/2C19 induction
Theophylline	CYP1A2 induction
Albendazole Antibacterial agents (doxycycline, rifampicin, tetracycline) Anticoagulants (warfarin, apixaban, dabigatran, edoxaban, rivaroxaban) Antifungal agents (azoles, posaconazole, voriconazole) Antiplatelets (ticagrelor) Cisatracurium Corticosteroids Cardiovascular agents (digoxin, nimodipine, quinidine) Delavirdine Furosemide Glibenclamide Hormones (oestrogens, oral contraceptives) (see sections 4.4 and 4.6) Lacosamide Lamotrigine Mexiletine Phenobarbital Psychotropic agents (paroxetine, clozapine, quetiapine) Rocuronium Sodium valproate [b] Valproic acid [b] Vitamin D	Unknown
Tenofovir alafenamide Afatinib	P-glycoprotein induction
[a] This list is not intended to be inclusive or comprehensive. Individual drug labels should be consulted. [b] Sodium valproate and valproic acid are similar medications. The term valproate has been used to represent these medications.	

Although not a true pharmacokinetic interaction, tricyclic antidepressants and phenothiazines may precipitate seizures in susceptible patients and Pro-Epanutin dosage may need to be adjusted.

Hyperammonemia with Concomitant Use of Valproate

Concomitant administration of phenytoin and valproate has been associated with an increased risk of valproate-associated hyperammonemia. Patients treated concomitantly with these two drugs should be monitored for signs and symptoms of hyperammonemia.

Pharmacodynamic interactions

Concomitant use of paroxetine or sertraline with phenytoin may lower the seizure threshold.

Phenytoin may increase serum glucose levels and therefore adjustment for insulin or oral antidiabetic agents (glibenclamide, tolbutamide) may be necessary.

Drug/Laboratory Test Interactions

Phenytoin may decrease serum concentrations of T_4. It may also produce low results in dexamethasone or metyrapone tests. This may be an artefact. Phenytoin may cause increased blood glucose or serum concentrations of alkaline phosphatase and gamma glutamyl transpeptidase (GGT). Phenytoin may affect blood calcium and blood sugar metabolism tests.

Phenytoin has the potential to lower serum folate levels.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to antiepileptic medicinal products in general
When possible, medical advice regarding the potential risks to a foetus caused by both seizures and antiepileptic treatment should be given to all women of childbearing potential taking antiepileptic treatment, and especially to women planning pregnancy and women who are pregnant. Antiepileptic treatment should be reviewed regularly and especially when a woman is planning to become pregnant. In pregnant women being treated for epilepsy, sudden discontinuation of antiepileptic drug (AED) therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. As a general principle, monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AEDs.

Risk related to phenytoin
Phenytoin crosses the placenta in humans. Similar concentrations of phenytoin have been reported in the umbilical cord and maternal blood.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. In humans, phenytoin exposure during pregnancy is associated with a frequency of major malformations 2 to 3 times higher than that of the general population, which has a frequency of 2-3%. Malformations such as orofacial clefts, cardiac defects, dysmorphic facial features, nail and digit hypoplasia, and growth abnormalities (including microcephaly) have been reported among children born to women with epilepsy who took phenytoin during pregnancy. Foetal toxicity, developmental toxicity and teratogenicity were observed in offspring of rats given fosphenytoin during pregnancy, similar to those reported with phenytoin (see section 5.3). Neurodevelopmental disorder has been reported among children born to women with epilepsy who took phenytoin alone or in combination with other AEDs during pregnancy. Studies related to neurodevelopmental risk in children exposed to phenytoin during pregnancy are contradictory and a risk cannot be excluded. There have been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. However, the respective role of antiepileptic drugs and other factors in the increased risk is not determined.

Pro-Epanutin should not be used in women of childbearing potential, women planning pregnancy, and pregnant women, except where there is a clinical need and when possible, the woman is made aware of the risks of taking fosphenytoin during pregnancy.

An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage (see section 4.2). However, postpartum restoration of the original dosage will probably be indicated.

In women of childbearing potential
Pro-Epanutin should not be used in women of childbearing potential unless other antiepileptic drugs are ineffective or not tolerated and when possible, the woman is made aware of the risk of potential harm to the foetus and the importance of planning pregnancy.

Women of childbearing potential should use effective contraception during treatment. Pregnancy testing in women of childbearing potential should be considered prior to initiating treatment with Pro-Epanutin.

Pro-Epanutin may result in a failure of hormonal contraceptives, hence women of childbearing potential should be counselled regarding the use of other effective contraceptive methods (see section 4.5).

Women planning to become pregnant and in pregnant women

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible. Pro-Epanutin should not be discontinued prior to reassessment of the treatment. When possible, patients should be informed of the potential harm to the foetus. If based on a careful evaluation of the risks and the benefits, Pro-Epanutin treatment is continued during the pregnancy, it is recommended to use the lowest effective dose and to institute specialized prenatal monitoring, oriented on the possible occurrence of the described malformations.

In neonates
Haemorrhagic syndrome has been reported in neonates born from epileptic mothers receiving phenytoin.Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother during the last gestational month and to the neonate after birth.

Post-natal monitoring/children
In case of exposure during pregnancy, children should be closely monitored in relation to neurodevelopmental disorders in order to provide specialized care as soon as possible, if necessary.

Breast-feeding

It is not known whether Pro-Epanutin is excreted in human milk. Following administration of oral phenytoin, phenytoin appears to be excreted in low concentrations in human milk. Therefore, breast-feeding is not recommended for women receiving Pro-Epanutin.

Fertility

In animal studies, fosphenytoin had no effect on fertility in male rats but decreased fertility in female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Caution is recommended in patients performing skilled tasks (e.g. driving or operating machinery) as treatment with fosphenytoin may cause central nervous system adverse effects such as dizziness and drowsiness (see section 4.8).

4.8 Undesirable effects

The following adverse events have been reported in clinical trials in adults receiving Pro-Epanutin. The list also includes adverse effects that have been reported spontaneously following both the acute and chronic use of phenytoin.

The more important adverse clinical events caused by the IV use of fosphenytoin or phenytoin are cardiovascular collapse and/or central nervous system depression. Hypotension can occur when either drug is administered rapidly by the IV route.

The adverse clinical events most commonly observed with the use of fosphenytoin in clinical trials were nystagmus, dizziness, pruritus, paraesthesia, headache**,** somnolence, and ataxia. With two exceptions, these events are commonly associated with the administration of IV phenytoin. Paraesthesia and pruritus, however, were seen much more often following fosphenytoin administration and occurred more often with IV fosphenytoin administration than IM fosphenytoin administration. These events were dose and rate related.

In the table below all adverse reactions, which occurred at an incidence greater than placebo and in more than one patient, are listed by class and frequency (very common (≥1/10), common (≥1/100, <1/10) uncommon (≥1/1,000, <1/100)) and Not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Additional reactions reported from post-marketing experience are included as frequency 'Not known'.

Blood and the lymphatic system disorders
Not known leukopenia, granulocytopenia, agranulocytosis, pancytopenia with or without bone marrow suppression, thrombocytopenia, aplastic anaemia, lymphadenopathy. Some of these reports have been fatal.

Immune system disorders
Not known anaphylactic/anaphylactoid reaction, hypersensitivity syndrome, periarteritis nodosa, immunoglobulin abnormalities, angioedema (see section 4.4).

Metabolism and nutrition disorders
Not known hyperglycaemia, appetite disorder

Psychiatric disorders
Common euphoric mood
Uncommon nervousness, confusional state, abnormal thinking

Nervous system disorders
Very common nystagmus, dizziness
Common paraesthesia, ataxia, somnolence, headache, tremor, abnormal coordination, dysgeusia, stupor, dysarthria
Uncommon hypoesthesia, reflexes increased, hyporeflexia
Not known extrapyramidal disorder, dyskinesia including chorea, dystonia and asterixis similar to those induced by phenothiazines or other neuroleptic drugs, drowsiness, motor twitching, insomnia, tonic seizures. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy. The incidence and severity of adverse events related to the CNS and sensory disturbances were greater at higher doses and rates.

Eye disorders
Common blurred vision, visual impairment
Uncommon diplopia

Ear and labyrinth disorders
Common tinnitus, vertigo
Uncommon hypoacusis

Cardiac disorders
Uncommon cardiac arrest
Not known severe cardiotoxic reactions with atrial and ventricular conduction depression (including bradycardia and all degrees of heart block), ventricular fibrillation and cardiovascular collapse (see section 4.4).

Vascular disorders
Common vasodilatation, hypotension

Respiratory, thoracic and mediastinal disorders
Not known pneumonitis, alterations in respiratory function including respiratory arrest. Some of these reactions have been fatal (see section 4.2).

Gastrointestinal disorders
Common nausea, dry mouth, vomiting
Uncommon hypoaesthesia of the tongue
Not known gingival hyperplasia, constipation

Hepatobiliary disorders
Not known toxic hepatitis, hepatocellular damage

Skin and subcutaneous tissue disorders
Very Common pruritus
Common ecchymosis
Uncommon rash. Other more serious and rare forms have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4).
Not known hirsutism, hypertrichosis, coarsening of the facial features, enlargement of the lips, Peyronie's disease, Dupuytren's contracture, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4), and urticaria.

Musculoskeletal and connective tissue disorders
Uncommon muscular weakness, muscle twitching, muscle spasms
Not known systemic lupus erythematosus, polyarthritis, Purple Glove Syndrome (see section 4.4).

Renal and urinary disorders
Not known interstitial nephritis

General disorders and administration site conditions
Common injection-site reaction, injection-site pain, asthenia, chills
Not known feeling of warmth or tingling in the groin

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with phenytoin. The mechanism by which phenytoin affects bone metabolism has not been identified.

Paediatric Population

The overall incidence and the types of adverse reactions in controlled clinical trials with IV administration of fosphenytoin to paediatric patients with epilepsy or neurosurgical patients were similar among children and adults treated with fosphenytoin. In an open-label, safety, tolerability, and pharmacokinetic study (982-028) of fosphenytoin in paediatric subjects (neonates through age 16), the following adverse reactions occurred at a frequency greater than 5% in 96 subjects treated with intravenous fosphenytoin: vomiting (20.8%), nystagmus (17.7%), ataxia (10.4%), fever (8.3%), nervousness (7.3%), pruritus (6.3%), somnolence (6.3%), hypotension (5.2%), and rash (5.2%).

No trends in laboratory changes were observed in Pro-Epanutin treated patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Nausea, vomiting, lethargy, tachycardia, bradycardia, asystole, cardiac arrest, hypotension, syncope, hypocalcaemia, metabolic acidosis and death have been reported in cases of overdosage with Pro-Epanutin.

Initial symptoms of Pro-Epanutin toxicity are those associated with acute phenytoin toxicity. These are nystagmus, ataxia and dysarthria. Irreversible cerebellar dysfunction and atrophy have been reported with phenytoin. Other signs include tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting, coma and hypotension. There is a risk of potentially fatal respiratory or circulatory depression. There are marked variations among individuals with respect to plasma phenytoin concentrations where toxicity occurs. Lateral gaze nystagmus usually appears at 20 mg/l, ataxia at 30 mg/l and dysarthria and lethargy appear when the plasma concentration is over 40 mg/l. However, phenytoin concentrations as high as 50 mg/l have been reported without evidence of toxicity. As much as 25 times the therapeutic phenytoin dose has been taken, resulting in plasma phenytoin concentrations over 100 mg/l, with complete recovery.

Treatment is non-specific since there is no known antidote to Pro-Epanutin or phenytoin overdosage. The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Haemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in children. In acute overdosage the possibility of the use of other CNS depressants, including alcohol, should be borne in mind.

Formate and phosphate are metabolites of fosphenytoin and therefore, may contribute to signs of toxicity following overdosage. Signs of formate toxicity are similar to those of methanol toxicity and are associated with severe anion-gap metabolic acidosis. Large amounts of phosphate, delivered rapidly, could potentially cause hypocalcaemia with paraesthesia, muscle spasms and seizures. Ionised free calcium levels can be measured and, if low, used to guide treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC-Code: N03AB

Pro-Epanutin is a prodrug of phenytoin and accordingly, its anticonvulsant effects are attributable to phenytoin.

The pharmacological and toxicological effects of fosphenytoin sodium include those of phenytoin.

The cellular mechanisms of phenytoin thought to be responsible for its anticonvulsant actions include modulation of voltage-dependent sodium channels of neurones, inhibition of calcium flux across neuronal membranes, modulation of voltage-dependent calcium channels of neurones and enhancement of the sodium-potassium ATPase activity of neurones and glial cells. The modulation of sodium channels may be a primary anticonvulsant mechanism because this property is shared with several other anticonvulsants in addition to phenytoin.

5.2 Pharmacokinetic properties

Fosphenytoin is a pro-drug of phenytoin and it is rapidly converted into phenytoin mole for mole.

Fosphenytoin Pharmacokinetics

Absorption/Bioavailability
When Pro-Epanutin is administered by IV infusion, maximum plasma fosphenytoin concentrations are achieved at the end of the infusion. Fosphenytoin is completely bioavailable following IM administration of Pro-Epanutin. Peak concentrations occur at approximately 30 minutes postdose. Plasma fosphenytoin concentrations following IM administration are lower but more sustained than those following IV administration due to the time required for absorption of fosphenytoin from the injection site.

Distribution
Fosphenytoin is extensively bound (95% to 99%) to human plasma proteins, primarily albumin. Binding to plasma proteins is saturable with the result that the fraction unbound increases as total fosphenytoin concentrations increase. Fosphenytoin displaces phenytoin from protein binding sites. The volume of distribution of fosphenytoin increases with fosphenytoin sodium dose and rate and ranges from 4.3 to 10.8 L.

Metabolism and Excretion
The hydrolysis of fosphenytoin to phenytoin yields 2 metabolites, phosphate and formaldehyde. Formaldehyde is subsequently converted to formate, which is in turn metabolised via a folate dependent mechanism. Although phosphate and formaldehyde (formate) have potentially important biological effects, these effects typically occur at concentrations considerably in excess of those obtained when Pro-Epanutin is administered under conditions of use recommended in this labelling.

The conversion half-life of fosphenytoin to phenytoin is approximately 15 minutes. The mechanism of fosphenytoin conversion has not been determined but phosphatases probably play a major role. Each mmol of fosphenytoin is metabolised to 1 mmol of phenytoin, phosphate and formate.

Fosphenytoin is not excreted in urine.

Phenytoin Pharmacokinetics (after Pro-Epanutin administration)
The pharmacokinetics of phenytoin following IV administration of Pro-Epanutin, are complex and when used in an emergency setting (e.g. status epilepticus), differences in rate of availability of phenytoin could be critical. Studies have, therefore, empirically determined an infusion rate for Pro-Epanutin that gives a rate and extent of phenytoin systemic availability similar to that of a 50 mg/min phenytoin sodium infusion. Because Pro-Epanutin is completely absorbed and converted to phenytoin following IM administration, systemic phenytoin concentrations are generated that are similar enough to oral phenytoin to allow essentially interchangeable use and to allow reliable IM loading dose administration.

The following table displays pharmacokinetic parameters of fosphenytoin and phenytoin following IV and IM Pro-Epanutin administration.

Mean Pharmacokinetic Parameter Values by Route of Pro-Epanutin Administration.

				Fosphenytoin	Total Phenytoin	Free (Unbound) Phenytoin

Route	Dose (mg PE)	Dose (mg PE/kg)	Infusion Rate (mg PE/min)	Cmax (µg/mL)	tmax (hr)	t½ (min)	Cmax (µg/mL)	tmax (hr)	Cmax (µg/mL)	tmax (hr)
Intramuscular	855	12.4	--	18.5	0.61	41.2	14.3	3.23	2.02	4.16
Intravenous	1,200	15.6	100	139	0.19	18.9	26.9	1.18	2.78	0.52
Intravenous	1,200	15.6	150	156	0.13	20.5	28.2	0.98	3.18	0.58

Dose = Fosphenytoin dose (phenytoin sodium equivalents [mg PE] or phenytoin sodium equivalents/kg [mg PE/kg]).
Infusion Rate = Fosphenytoin infusion rate (mg phenytoin sodium equivalents/min [mg PE/min]).
Cmax = Maximum plasma analyte concentration (µg/mL).
Tmax = Time of Cmax (hr).
t½ = Terminal elimination half-life (min).

Absorption/Bioavailability
Fosphenytoin sodium is rapidly and completely converted to phenytoin following IV or IM Pro-Epanutin administration. Therefore, the bioavailability of phenytoin following administration of Pro-Epanutin is the same as that following parenteral administration of phenytoin.

Distribution
Phenytoin is highly bound to plasma proteins, primarily albumin, although to a lesser extent than fosphenytoin. In the absence of fosphenytoin, approximately 12% of total plasma phenytoin is unbound over the clinically relevant concentration range. However, fosphenytoin displaces phenytoin from plasma protein binding sites. This increases the fraction of phenytoin unbound (up to 30% unbound) during the period required for conversion of fosphenytoin to phenytoin (approximately 0.5 to 1 hour post infusion).

The volume of distribution for phenytoin ranges from 24.9 to 36.8 L.

Metabolism and Excretion
Phenytoin derived from administration of Pro-Epanutin is extensively metabolised in the liver and excreted in urine primarily as 5-(p-hydroxy-phenyl)-5-phenylhydantoin and its glucuronide; little unchanged phenytoin (1%-5% of the Pro-Epanutin dose) is recovered in urine. Phenytoin hepatic metabolism is saturable and, following administration of single IV Pro-Epanutin doses of 400 to 1,200 mg PE, total and unbound phenytoin AUC values increase disproportionately with dose. Mean total phenytoin half-life values (12.0 to 28.9 hr) following Pro-Epanutin administration at these doses are similar to those after equal doses of parenteral phenytoin and tend to be longer at higher plasma phenytoin concentrations.

Characteristics in Patients

Patients with renal or hepatic disease:
Fosphenytoin conversion to phenytoin is more rapid in patients with renal or hepatic disease than with other patients because of decreased plasma protein binding, secondary to hypoalbuminaemia, occurring in these disease states. The extent of conversion to phenytoin is not affected. The fraction of unbound phenytoin is increased in patients with renal or hepatic disease, or in those with hypoalbuminaemia. Unbound concentration of phenytoin may be elevated in patients with hyperbilirubinaemia. Phenytoin metabolism may be reduced in patients with hepatic impairment resulting in increased plasma phenytoin concentrations(see section 4.2).

Elderly patients:
Patient age had no significant impact on fosphenytoin pharmacokinetics. Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20-30 years of age) (see section 4.2).

Gender:
Gender had no significant impact on fosphenytoin or phenytoin pharmacokinetics.

Paediatric population:
Limited studies in children (age 5 to 10) receiving Pro-Epanutin have shown similar concentration-time profiles of fosphenytoin and phenytoin to those observed in adult patients receiving comparable mg PE/kg doses.

5.3 Preclinical safety data

The systemic toxicity of fosphenytoin is qualitatively and quantitatively similar to that of phenytoin at comparable exposures.

Carcinogenicity studies with fosphenytoin are unavailable. Since fosphenytoin is a prodrug of phenytoin, the carcinogenicity results with phenytoin can be extrapolated. Carcinogenicity studies in mice have shown an increased incidence of hepatocellular tumours at phenytoin plasma concentrations approximating the therapeutic range. Similar studies in rats have shown an inconsistent increase in hepatocellular tumours. The clinical significance of these findings is unknown.

Genetic toxicity studies showed that fosphenytoin was not mutagenic in bacteria or in mammalian cells in vitro. It is clastogenic in vitro but not in vivo.

Fetal toxicity, developmental toxicity and teratogenicity occurred in offspring from rats given fosphenytoin prior to and during mating, gestation, and lactation. No developmental effects were observed in offspring of pregnant rabbits given fosphenytoin; malformations have been reported in offspring of pregnant rabbits given phenytoin. Perinatal/postnatal effects in rats include decreased growth of offspring and behavioural toxicity. Fosphenytoin had no effect on fertility in male rats. In females, altered oestrous cycles, prolonged gestation, and delayed mating were observed.

Local irritation following IV or IM dosing or inadvertent perivenous administration was less severe with fosphenytoin than with phenytoin and was generally comparable to that observed with vehicle injections. The potential of fosphenytoin to induce intra-arterial irritation was not assessed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Water for injection,
- Trometamol buffer,
- Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C- 8°C).The undiluted product may be stored at room temperature (8°C to 25°C) for up to 24 hours.

6.5 Nature and contents of container

5 and 10 mL untreated Type I clearglass vials (containing 2 and 10 mL solution, respectively) with a Fluorotec coated stopper, and an aluminium seal with flip-off cap.

Boxes of 5 vials with 2 mL solution.

Boxes of 10 vials with 2 mL solution.

Boxes of 25 vials with 2 mL solution.

Boxes containing 10 boxes of 5 vials (=50 vials) with 2 mL solution.

Boxes of 5 vials with 10 mL solution.

Boxes of 10 vials with 10 mL solution.

Boxes containing 5 boxes of 5 vials (=25 vials) with 10 mL solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Pro-Epanutin must be diluted to a concentration ranging from 1.5 to 25 mg PE/mL prior to infusion, with 5% glucose or 0.9% saline solution for injection (see section 4.2). After dilution Pro-Epanutin is suitable only for immediate use.

For single use only. After opening, unused product should be discarded.

Vials that develop particulate matter should not be used.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

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