IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0540/131/001
Case No: 2067670

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

sanofi-aventis Ireland Limited

Citywest Business Campus, **Dublin 24**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Vallergan Forte 30 mg / 5 ml Oral Solution.

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **22/02/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vallergan Forte 30 mg / 5 ml Oral Solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of oral solution contains 30 mg of Alimemazine (Trimeprazine) Tartrate.

Excipients:	Sucrose	3.40 g / 5ml
	Sodium sulphite anhydrous (E221)	5.0 mg / 5ml
	Sodium metabisulphite (E223)	5.0 mg / 5ml
	Ethanol (96% v/v)	201.5 mg / 5ml

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral solution.

A clear, colourless to very pale yellow solution with an odour of apricots.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. In the management of urticaria, pruritus (including that associated with obstructive jaundice) and senile pruritus.

2. In short term sedation and pre-anaesthetic medication in children.

4.2 Posology and method of administration

The route of administration is oral.
For use in adults and children over 2 years of age.
Use a measuring cup or measuring pipette, which should be held vertically.
Recommended dosage:

Urticaria and Pruritus

Adults:
The usual total daily dosage is 30 to 40 mg in divided doses.
Children:
The usual total daily dosage is 7.5 to 20 mg in divided doses.
Dosing may be repeated as needed during the day not to exceed 4 daily doses.
Evening dosing is preferable due to the pronounced sedative effect of alimemazine.

For sedation
Children:
Aged 7 to 12 years:
60 to 90 mg daily in divided doses.
Aged 3 to 6 years:
15 to 60 mg daily in divided doses.

Use should be for as short a period as possible.

Pre-anaesthetic medication (children aged 2-7 years): The maximum dosage recommended for this indication in children is 2 mg per kg.

4.3 Contraindications

- Use in patients hypersensitive to the active ingredient or any of the excipients.
- Use in patients with hepatic or renal dysfunction, epilepsy, Parkinsons disease, hypothyroidism, phaeochromocytoma, myasthenia gravis, prostatic hypertrophy.
- Use in patients with a history of narrow angle glaucoma.
- Use in patients with a history of agranulocytosis associated with other phenothiazines.
- Children under 6 years of age
- Use in patients with coma particularly if associated with other central nervous system depressants.
- Use in patients on concurrent therapy with other drugs potentially haemotoxic.
- Sultopride (see Interactions).
- Pregnant women (1^{st} trimester) or nursing mothers (see Pregnancy and Lactation).

4.4 Special warnings and precautions for use

Phenothiazines should not be used in children under 2 years of age.
Alimemazine should be used with caution in:

- Elderly patients presenting:

- greater susceptibility to orthostatic hypotension, dizziness and sedative effects,
- chronic constipation (risk of paralytic ileus),
- possible prostatic hypertrophy

- Patients with severe hepatic and/or renal insufficiency (risk of accumulation).

The tablet form is reserved for use in adults and children over 6 years of age. Monitoring (of clinical and possible EEG parameters) should be intensified in epileptic patients because phenothiazines and terpene derivatives (menthol) may lower the seizure threshold.

- Allergic manifestations:

In the event of persistence or worsening of allergic symptoms (respiratory distress, oedema, skin lesions, etc) or signs associated with viral infection, the clinical approach should be re-evaluated.

Phenothiazines should only be used with great caution in patients with a history of jaundice or with existent liver dysfunction or blood dyscrasias.

Patients receiving phenothiazines over a prolonged period require regular and careful surveillance with particular attention to potential for inducing eye changes, effects on haemopoiesis, liver dysfunction, myocardial conduction defects, particularly if other concurrently administered drugs also have potential effects on these systems.

Phenothiazines should be used with particular care in the presence of extremes of temperature because of its capacity to interfere with the body's thermoregulator.

Phenothiazines produce a photosensitizing effect, therefore exposure to sunlight should be avoided during treatment.

The sugar content should be considered in patients with diabetes or on low-sugar diets.

Patients are strongly advised not to consume alcoholic beverages or medicines containing alcohol during treatment. Avoid concomitant use of neuroleptics. (See Interactions).

Phenothiazines should be used with great caution in patients with coronary insufficiency or cardiac disease, due to the tachycardia- inducing and hypotensive effects of phenothiazines (See section 4.8). As with other neuroleptic phenothiazines, caution is advised in patients with a family history of QT prolongation.

(Galactorrhoea) Lactation and amenorrhoea are rare and tend to be dose dependant, and may be related to increased secretion or prolaction.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

There is a risk of post operative restlessness especially if the child is in pain.

4.5 Interaction with other medicinal products and other forms of interaction

Inadvisable combinations:
Alcohol: Alcohol enhances the sedative effect of H_1 antihistamines. Impaired alertness may be hazardous for driving and operating machines. Do not consume alcoholic beverages or take medicines containing alcohol.

Sultopride: Increased risk of ventricular rhythm disorders, particularly torsades de pointes, due to additive electrophysiological effects.

Disulfiram; cefamandole, cefoperazone, latamoxef (cephalosporin antibacterial agents); chloramphenicol (phenicol antibacterial agent); chlorpropamide, glibenclamide, glipizide, tolbutamide (hypoglycaemic sulphonamide antidiabetic agents); griseofulvin (antifungal agent); metronidazole, ornidazole, secnidazole, tinidazole (5 nitroimidazoles); ketoconazole (azole antifungal agent); procarbazine (cytostatic agent): medicines producing antabuse reactions with alcohol (heat, redness, vomiting, tachycardia). Do not consume alcoholic beverages or take medications containing alcohol.

Combinations to take into consideration:

Other central nervous system depressants: sedative antidepressants, barbiturates, benzodiazepines, clonidine, and related drugs, hypnotics, morphine derivatives (analgesics and antitussives), methadone, neuroleptics, anxiolytics: increased CNS depression.
Impaired alertness may be hazardous for driving and using machines.

Atropine and atropine-like drugs (imipramine-like antidepressants, anticholinergic antiparkinsonian agents, atropine-like antispasmodics, disopyramide, phenothiazine neuroleptics): additive atropine-like adverse effects of the type urinary retention, constipation, dry mouth.

The concomitant administration of this product with other medications such as central nervous system depressant (including alcohol and anaesthetics), or antihypertensives or anticholinergics will result in accentuation of their effects, while potentiation of action will also occur with monoamine oxidase inhibitors, antidepressants and analgesics.

The hypotensive effect of phenothiazines may potentiate the effects of antihypertensives, or of other drugs with hypotensive activity.

The drug may intensify by increasing the effects of Parkinson’s disease.

Simultaneous administration of prochlorperazine and desferrixoamine has been observed to induce a transient metabolic encephalopathy characterised by loss of consciousness for 48-72 hours. This may occur with trimeprazine since it shares many of the pharmacological activities of prochlorperazine.

As with other neuroleptic phenothiazines, caution is advised with concomitant use of QT prolonging drugs or drugs that cause electrolyte imbalance.

4.6 Pregnancy and lactation

Risk of malformations:

- There are no reliable data on tetraogenic effects in animals
- Currently, there are no data sufficiently relevant to assess the potential risk of malformations or foetotoxic effects when alimemazine is used during pregnancy.

Risk of foetotoxicity:
There have been rare reports of gastrointestinal disturbances related to atropine-like properties (abdominal distension, meconium ileus, delayed meconium excretion, difficulty in feeding initiation, tachycardia, neurological disorders, etc.) in neonates whose mothers had received long term treatment with high doses of anticholinergic drugs. In view of these data, this drug should not be used during the first trimester of pregnancy. It should only be used after the first trimester, if necessary, and given only on an occasional basis in the third trimester.
If this drug is used at pregnancy term, a period of monitoring of the neurological and gastrointestinal function of the neonate appears warranted.

It is not known whether alimemazine is excreted into the maternal milk. In view of potential sedation or paradoxical excitation of the neonate and particularly considering the risks of sleep apnoea associated with phenothiazines, this drug should not be used by nursing mothers.

4.7 Effects on ability to drive and use machines

Phenothiazines may induce drowsiness especially at the start of the treatment. Persons taking these drugs should not drive or operate machinery unless the drug has been shown not to interfere with physical or mental ability.

4.8 Undesirable effects

Autonomic effects:

- sedation or drowsiness, more marked at the start of treatment;
- anticholinergic effects such as dry mouth, constipation, accommodation disorders, mydriasis, cardiac palpitations, risk of urinary retention;
- orthostatic hypotension (particularly elderly and volume depleted subjects)
- balance disorders, dizziness, impaired memory or concentration;
- lack of motor coordination, tremor (more frequent in elderly patients);
- mental confusion, hallucinations;
- more rarely, but notably in infants: excitation-type effects: agitation, nervousness, insomnia.

Sensitization reactions:

- erythema, eczema, pruritus, purpura, urticaria (including giant urticaria);
- oedema, more rarely: Quinckes (angioneurotic) oedema;
- anaphylactic shock;
- photosensitization.

Skin and Eyes: Contact skin sensitisation is a serious but rare complication in those frequently handling preparations of phenothiazines. The greatest care must be taken to avoid contact of the drug with the skin. Skin rashes of various kinds may also be seen in patients treated with the drug.

Haematological effects

- leucopenia, neutropenia, exceptionally: agranulocytosis;
- thrombocytopenia;
- haemolytic anaemia.

The occurrence of unexplained infections or fever requires immediate haemotological investigation

Liver Function: Jaundice, occurs in a very small percentage of patients taking neuroleptics. A premonitary sign may be a sudden onset of fever after one three weeks of treatment followed by the development of jaundice. Neuroleptic jaundice has a biochemical and other characteristics of obstructive jaundice and is associated with obstruction of the canaliculi by bile thrombi, frequent presence of an accompanying eosinophilia indicates the allergic nature of this phenomenon. Treatment should be withheld on the development of jaundice.

Cardiorespiratory:
Cardiac arrhythmias, including atrial arrhythmia, A-V block, ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) have been reported during neuroleptic therapy, possible related to dosage. Pre- existing cardiac disease, old age, hypokalaemia and concurrent tricyclic anti – depressants may predispose. ECG changes, usually benign, include QT interval prolongation, ST depression, U waves and T waves changes. Sudden unexplained death, cardiac arrest, Torsades de pointes have been reported with the class of neuroleptics.

Respiratory depression is possible in susceptible patients.

Extrapyramidal : acute dystonias or dyskinesias, usually transitory are commoner in children and young adults and usually occurs within the first four days of treatment or after dosage increases.

Akathisia characteristically occurs after large initial doses.

Parkinsonism is commoner in adults and the elderly. It usually develops after weeks or months of treatment. One or more f the following may be seen: tremor, rigidity, akinesia or other features of Parkinsonism. Commonly just tremor.

Tardive dyskinesia : if this occurs it is usually, though not necessarily after prolonged or high dosage. It can even occur after treatment has been stopped.

Dosage should therefore be kept low whenever possible.

Endocrine: Hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhoea, impotence.

Neuroleptic malignant syndrome: Hyperthermia, rigidity, autonomic dysfunction and altered consciousness may occur with any neuroleptic.

A minor side effect is nasal stuffiness.

4.9 Overdose

Symptoms of phenothiazine overdosage include drowsiness or loss of consciousness, hypotension, tachycardia, E.C.G. changes, ventricular arrhythmias and hypothermia. Severe extra-pyramidal dyskinesias may occur.

If the patient is seen sufficiently soon (up to 6 hours) after ingestion of a toxic dose, gastric lavage should be attempted. Pharmacological induction of emesis is unlikely to be of any use. Activated charcoal should be given. There is no specific antidote. Treatment is supportive.

Generalised vasodilatation may result in circulatory collapse, raising the patient's legs may suffice, in severe cases, volume expansion by intravenous fluids may be needed; infusion fluids should be warmed before administration in order not to aggravate hypothermia.

Positive ionotropic agents such as dopamine may be tried if fluid replacement is insufficient to correct the circulatory collapse. Peripheral vasoconstrictor agents are not generally recommended; avoid the use of adrenaline.

Ventricular or supraventricular tachy-arrhythmias usually respond to restoration of normal body temperature and correction of circulatory or metabolic disturbances. If persistent or life threatening, appropriate anti-arrhythmic therapy may be considered.

Avoid lignocaine and, as far as possible, long acting anti-arrhythmic drugs.
Pronounced central nervous system depression requires airway maintenance or, in extreme circumstances, assisted respiration. Severe dystonic reactions usually respond to procyclidine (5-10 mg) or orphenadrine (20-40 mg) administered intramuscularly or intravenously. Convulsions should be treated with intravenous diazepam.

Neuroleptic malignant syndrome should be treated with cooling. Dantrolene sodium should be tried.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Trimeprazine, a phenothiazine derivative, has a central sedative effect comparable to that of chlorpromazine, but is largely devoid of the latter's anti-adrenaline action. It has powerful antihistamine and antiemetic actions.

5.2 Pharmacokinetic properties

A phenothiazine, well absorbed but metabolised in gut wall and in liver. Distribution is wide, elimination occurs in bile and urine with prolonged half-life.

5.3 Preclinical safety data

None.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid sugar Gran Liquors (containing sucrose and water)
Apricot Flavour No.1 (containing flavour, isopropyl alcohol and water)
Ethanol 96% v/v
Citric Acid Anhydrous
Sodium Citrate
Sodium Benzoate (E211)
Sodium Sulphite Anhydrous (E221)
Sodium Metabisulphite (E223)
Ascorbic Acid
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.
Use within one month of opening bottle.

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton.

6.5 Nature and contents of container

Vallergan Forte is supplied in amber Type III bottles with an aluminium lid with a polyethylene liner with a tamper evident band or with a polypropylene child proof cap with a polyethylene liner. This product is available in 100 ml bottles**.**

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Vallergan Forte may be diluted if required, using simple syrup, (without preservatives).

7 MARKETING AUTHORISATION HOLDER

sanofi-aventis Ireland Ltd.
Citywest Business Campus
Dublin 24.

8 MARKETING AUTHORISATION NUMBER

PA 540/131/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1977

Date of last renewal: 05 June 2006

10 DATE OF REVISION OF THE TEXT

February 2010