Public Assessment Report

Decentralised Procedure

Alimemazine tartrate 7.5mg/5ml Syrup

Alimemazine tartrate 30mg/5ml Syrup

Procedure No: UK/H/4750/001-002/DC

UK Licence No: PL 41830/0029-0030

NRIM Limited
This is a summary of the Public Assessment Report (PAR) for Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup (PL 41830/0029-0030; UK/H/4750/001-002/DC). It explains how the applications for Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup.

For practical information about using Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup, patients should read the package leaflet or contact their doctor or pharmacist.

What are Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup and what are they used for?
Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup are ‘generic medicines’. This means that they are similar to ‘reference medicines’ already authorised in the European Union (EU) called Vallergan Syrup 7.5mg/5ml and 30mg/5ml (Winthrop Pharmaceuticals Ltd), which were authorised on 1 July 1998.

Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup are used to treat itching (pruritus) or an itchy, lumpy rash (urticaria). The 7.5mg/5ml syrup only should be used to treat these conditions in children.

The 30mg/5ml syrup is used as a sedative before anaesthesia for children aged between 2 and 7 years (to reduce awareness or make the child feel relaxed and at ease before an operation).

How do Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup work?
Alimemazine tartrate belongs to a group of medicines called phenothiazines. It works by blocking a natural substance (histamine) that the body makes during an allergic reaction. It also works directly on the brain to help the patient feel more relaxed.

How are Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup used?
Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup should be swallowed. These medicines are provided with a 2 ml graduated dosing syringe and syringe adaptor to allow accurate dosing. Patients should check with their doctor if they are not sure how to take the syrup.

The syrup should not be touched for longer than is necessary, as this can cause skin redness, swelling and itching (contact skin sensitisation).

Patients should read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup can only be obtained with a prescription.

What benefits of Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup have been shown in studies?
No studies were needed because Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup are generic medicines that are taken as oral solutions and contain the same active substances as their respective reference medicines, Vallergan Syrup 7.5mg/5ml and 30mg/5ml.
What are the possible side effects of Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup?

Because Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup are generic medicines their possible side effects are taken as being the same as those of the reference medicines.

For the full list of all side effects reported with Alimemazine tartrate 7.5mg/5ml Syrup and 30mg/5ml, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why are Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup approved?

It was concluded that, in accordance with EU requirements, Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup have been shown to be comparable to Vallergan Syrup 7.5mg/5ml and 30mg/5ml. Therefore, the MHRA decided that, as for Vallergan Syrup 7.5mg/5ml and 30mg/5ml, the benefits outweigh the identified risks and recommended that Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup can be approved for use.

What measures are being taken to ensure the safe and effective use of Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup?

A risk management plan has been developed to ensure that Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup

Marketing Authorisations were granted in the UK for Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup on 16 January 2014.

The full PAR for Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup follows this summary.

For more information about treatment with Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in March 2015.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th></th>
<th>Introduction</th>
<th>Page 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>Page 6</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>Page 10</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>Page 10</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
<td>Page 12</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and recommendation</td>
<td>Page 12</td>
</tr>
</tbody>
</table>

Annex 1 - Table of content of the PAR update for MRP and DCP | Page 14
Scientific discussion

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Competent Authorities of Ireland and the UK considered that the applications for Alimemazine tartrate 7.5mg/5ml Syrup and Alimemazine tartrate 30mg/5ml Syrup (PL 41830/0029-0030; UK/H/4750/001-002/DC) could be approved. These are prescription-only medicines (POMs).

Alimemazine has powerful antihistamine and anti-emetic actions and is used in the management of urticaria and pruritus. Alimemazine tartrate 7.5mg/5ml Syrup should be used for this indication in children.

Alimemazine may be used in pre-medication as a sedative before anaesthesia in children aged between 2 to 7 years. Alimemazine tartrate 30mg/5ml Syrup can be used for the specific indication of pre-anaesthesia sedation in children.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). The applications for Alimemazine tartrate 7.5mg/5ml Syrup and Alimemazine tartrate 30mg/5ml Syrup were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. Alimemazine tartrate 7.5mg/5ml Syrup and Alimemazine tartrate 30mg/5ml Syrup cross-refer to the reference medicinal products Vallergan Syrup 7.5mg/5ml and 30mg/5ml (PL 17780/0465 and PL 17780/0466; Winthrop Pharmaceuticals Limited), which were first authorised in the UK on 1 July 1998.

Alimemazine is a histamine H₁ receptor antagonist belonging to the antihistamine category. Alimemazine (previously known as trimeprazine) is a tricyclic antihistamine, similar in structure to the phenothiazine antipsychotics, but differing in the ring-substitution and chain characteristics. Alimemazine competes with free histamine for binding to the histamine H₁ receptor and therefore blocks histamine-mediated symptoms such as itching. Alimemazine has a central sedative effect comparable to that of the related drug chlorpromazine but is largely devoid of the latter’s anti-adrenaline action. Alimemazine also has anti-emetic actions.

No new non-clinical or clinical data were submitted, which is acceptable given that the applications are for oral solutions which are generic medicinal products of originator products that have been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of the product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The UK and Ireland considered that the application could be approved at the end of procedure (Day 209) on 27 November 2014. After a subsequent national phase, a licence was granted to NRIM Limited in the UK on 16 January 2015.
II QUALITY ASPECTS

II.1 Introduction
Alimemazine tartrate 7.5mg/5ml Syrup and Alimemazine tartrate 30mg/5ml Syrup are clear, colourless to pale yellow, syrupy liquids containing 1.5mg and 6mg alimemazine tartrate per 1ml dose, respectively. The excipients in the medicinal products are sucrose, ethanol, citric acid monohydrate, anhydrous (E330), sodium benzoate (E211), sodium sulphite anhydrous (E221), sodium metabisulphite (E223), ascorbic acid (E300), apricot flavour, caramel flavour sodium citrate (E331).

The syrups are presented in 100ml amber glass bottles with a white tamper evident child-resistant plastic cap. A 2 ml graduated dosing syringe and syringe adapter are also provided.

II.2 DRUG SUBSTANCE – ALIMEMAZINE TARTRATE
INN: Alimemazine tartrate
Chemical name: (2RS)-N,N,2-Trimethyl-3-(10H-phenothiazin-10-yl)propan-1-amine hemi[(2R,3R)-2,3-dihydroxybutanedioate].

Structure:

Molecular formula: C_{20}H_{25}N_{2}O_{3}S
Molecular weight: 373.5
Appearance: White or very slightly yellowish powder
Solubility Freely soluble in water, sparingly soluble in ethanol (96 per cent) and practically insoluble in toluene

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
II.3 MEDICINAL PRODUCTS

Pharmaceutical Development
The aim of the pharmaceutical development of Alimemazine tartrate 7.5mg/5ml Syrup and Alimemazine tartrate 30mg/5ml Syrup was to develop generic versions of the innovator products, Vallergan Syrup 7.5mg/5ml and 30mg/5ml.

All the excipients comply with their respective European Pharmacopoeia monographs, with the exception of ethanol, sodium benzoate (E211) and sodium metabisulphite (E223), which comply with their respective British Pharmacopoeia monographs and apricot flavour, caramel flavour, which are controlled in line with suitable in-house specifications.

Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. Based on pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production batches.

Control of Finished Products
The finished product specifications are acceptable. Test methods have been described and have been validated adequately. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Products
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life 24 months with the storage precaution ‘Store in the original package in order to protect from light’ has been approved.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted for Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup.

II.5 Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPCs and PIL are available on the MHRA website. The current labelling is presented below:
Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup

**Label:**

Each 1ml contains 1.5mg of alimemazine tartrate.
Also contains sucrose, ethanol, sodium sulphite (E223), sodium metabisulphite (E223) and sodium chloride (E351).
For oral use.
Read the package leaflet before use.
Keep out of the sight of children.
Exposure of the skin to sunlight must be avoided.
Store in the original package in order to protect from light.
Once opened, use within one month.
Use as directed by your physician.

**Carton:**

100ml Syrup
A 2 ml graduated dosing syringe and syringe adapter are provided for accurate dosing.
Alimemazine tartrate 30mg/5ml Syrup

Label:

Each 5ml contains: Alimemazine tartrate.
Also contains sucrose, ethanol, sodium sulphite (E225), sodium metabisulphite (E223) and sodium citrate (E331).

For oral use. Read the package leaflet before use.

Keep out of the sight and reach of children.

Exposure of this product to sunlight must be avoided.

Store in the original packaging in order to protect from light.

Once opened, use within one month.

Use as directed by your physician.

Carton:

A 2 ml graduated dosing syringe and syringe adapter are provided for accurate dosing.
III NON-CLINICAL ASPECTS

IV

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of alimemazine tartrate are well-known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable, see Section III.1 Introduction, above.

III.3 Pharmacokinetics
Not applicable, see Section III.1 Introduction, above.

III.4 Toxicology
Not applicable, see Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the products are intended for generic substitution with products that are already marketed, no increase in environmental exposure to alimemazine tartrate is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that Marketing Authorisations are granted for Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction.
No new clinical data have been submitted and none are required for an application of this type. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
In accordance with the guideline on the investigation of bioequivalence the applicant is not required to submit a therapeutic equivalence study if the product is to be taken as an oral solution with the same active substance, in the same concentration as the reference product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions). Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup do not contain any excipients that would affect absorption, in vivo solubility or stability of the active substance.

IV.3 Pharmacodynamics
The clinical pharmacodynamics properties of alimemazine tartrate are well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy
The clinical efficacy of alimemazine tartrate is well-known. No new efficacy data are presented or are required for this type of application.
IV.5 Clinical Safety
The clinical safety of alimemazine tartrate is well-known. No new safety data were submitted and none are required for this type of application.

IV.6 Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup.

A summary of safety concerns is listed in the table below:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
</tr>
<tr>
<td>Use in patients with hepatic or renal dysfunction.</td>
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<tr>
<td>Exacerbation of symptoms in patients who suffer from epilepsy, Parkinson’s disease, hypothyroidism, phaeochromocytoma, myasthenia gravis, prostatic hypertrophy.</td>
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<tr>
<td>Hypersensitivity reactions to phenothiazines.</td>
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<td>Deterioration in vision in patients with history of narrow angle glaucoma</td>
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<tr>
<td>Postural hypotension in children and in elderly patients or volume depleted patients.</td>
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<tr>
<td>Ileus when used in elderly patients with chronic constipation</td>
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<tr>
<td>Tachycardia when used in patients with certain cardiovascular diseases</td>
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<tr>
<td>Skin sensitisation and photosensitivity reaction upon exposure to sunlight</td>
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<tr>
<td>Extrapyramidal side effects, especially in children or young adults.</td>
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<td>Leukopaenia and agranulocytosis</td>
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<td>Drowsiness which may have an effect on the ability to drive and operate machinery.</td>
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<tr>
<td>Use in pregnancy and lactation.</td>
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<tr>
<td><strong>Important potential risks</strong></td>
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<td>Failure of thermoregulation with hypothermia or hyperthermia when used in the presence of extremes of temperature</td>
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<td>Increased sedative effect in patients who consume alcohol or those taking medicines containing alcohol, on anxiolytics, hypnotics, opiates, barbiturates or other sedatives</td>
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<tr>
<td>Increased sedative effect and risk of respiratory depression when used in patients on tricyclic antidepressants and Monoamine Oxidase Inhibitors (MAOIs)</td>
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<td>Exaggerated hypotensive effect when used in patients taking antihypertensive drugs</td>
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<tr>
<td>Increased anticholinergic effects when used in patients taking anticholinergic drugs.</td>
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<td>Reduced efficacy of the following treatments: amphetamine, levodopa, clonidine, guanethidine or adrenaline.</td>
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<tr>
<td>Reduced response to hypoglycaemic agents with</td>
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<tr>
<td>Summary of safety concerns</td>
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| Important missing information | • None |

The Applicant proposes routine Pharmacovigilance and routine risk minimisation measures for all safety concerns, which is accepted.

### IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup.

### V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

### VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

#### QUALITY

The important quality characteristics of Alimemazine tartrate 7.5mg/5ml and 30mg/5ml Syrup are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

#### NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of alimemazine tartrate are well-known, no additional data were required.

#### EFFICACY

No new data were submitted and none are required for this type of application.

#### SAFETY

No new data were submitted and none are required for this type of application.

#### PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.
BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with alimemazine tartrate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of Marketing Authorisations is recommended.
Annex 1 - Table of content of the PAR update for MRP and DCP

**Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report**
(Type II variations, PSURs, commitments)

<table>
<thead>
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<th>Date of end of procedure</th>
<th>Approval / non approval</th>
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