2.5 Clinical Overview

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2.5.1 PRODUCT DEVELOPMENT RATIONAL

2.5.1.1 PHARMACOLOGICAL CLASS

Levomepromazine or methotrimeprazine is a phenothiazine aliphatic antipsychotic with the molecular formula $C_{19}H_{25}N_2OS$. Levomepromazine, therefore, belongs to the phenothiazine group of drugs, like chlorpromazine. Phenothiazines have a three-ring structure in which two benzene rings are linked by a sulphur and nitrogen atom. Levomepromazine's chemical structure is (–)(dimethylamino-3 methyl-2 propyl)-10 methoxy-2 phenothiazine (Figure 1) [1].

Table I: Chemical data and Identifiers of Levomepromazine and Levomepromazine hydrochloride

Chemical Data		
Name	Levomepromazine Levomepromazine hydrochloride	
Synonyms	Methotrimeprazine Methotrimeprazine hydrochloride	
IUPAC Name	(2R)-3-(2-methoxyphenothiazin-10-yl)-N,N,2-trimethylpropan-1-amine (levomepromazine) (2R)-3-(2-methoxyphenothiazin-10-yl)-N,N,2-trimethylpropan-1-amine;hydrochloride (Levomepromazine hydrochloride)	
Chemical Formula	$C_{19}H_{24}N_2OS$ (Levomepromazine) $C_{19}H_{25}ClN_2OS$ (Levomepromazine hydrochloride)	
Mol. Mass	328.474 g/mol (Levomepromazine) 364.9 g/mol (Levomepromazine hydrochloride)	
Identifiers		
CAS number	60-99-1 (Levomepromazine) 1236-99-3 (Levomepromazine hydrochloride)	
ATC code	N05AA02	
ATC Groups	*1st Level*	N: Nervous System
	2nd Level	N05: Psycholeptics
	3rd Level	N05A: Antipsychotics
	4th Level	N05AA: Phenothiazines with aliphatic side chain
PubChem	72287 (Levomepromazine) 11954230 (Levomepromazine hydrochloride)	
IUPHAR/BPS	7603 (Levomepromazine)	
DrugBank	DB01403 (Levomepromazine)	
ChemSpider	65239 (Levomepromazine) 10128525 (Levomepromazine hydrochloride)	
UNII	9G0LAW7ATQ (Levomepromazine) 42BB1Y2586 (Levomepromazine hydrochloride)	
KEGG	D00403 (Levomepromazine) D01520 (Levomepromazine hydrochloride)	
ChEMBL	ChEMBL1764 (Levomepromazine) CHEMBL2104973 (Levomepromazine hydrochloride)	
ECHA InfoCard	100.000.450 (Levomepromazine) 100.013.617 (Levomepromazine hydrochloride)	

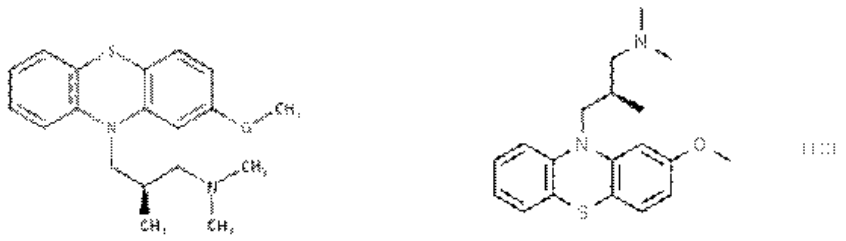

Figure 1: Chemical structure of Levomepromazine (on the left) and levomepromazine hydrochloride (on the right) [1]

2.5.1.2 INFORMATION ABOUT THE CONDITION

Levomepromazine is indicated for the following conditions:

- the suppression of psychomotor restlessness and agitation within the context of psychotic disorders
- acute agitation states in manic episodes
- as an adjunct therapy for the treatment of severe and/or chronic pain

Levomepromazine possesses anti-emetic effects as discussed in Section 2.5.4.3.1. The above claimed indications for the product under assessment are the same with the indications of the reference product Neurocil Tropfen, 40 mg/ml, Tropfen zum Einnehmen, Lösung.

Agitation is a transnosological syndrome. This cluster of pathological behaviour occurs in a variety of psychiatric diseases including schizophrenia, bipolar disorder, or dementia. Agitation represents a poorly organized and aimless psychomotor activity stemming from physical or mental unease [2]. Motor restlessness, increased responsiveness to external or internal stimuli, irritability, inappropriate and usually purposeless verbal and motor activity are the major hallmarks of the syndrome. It can readily result into a verbal or physical aggression toward objects or persons and the patients may then pose a danger to others. By definition, violence is a physical aggressive behaviour that is intended to inflict harm to other people. While acute aggressive behaviour occurs as a state phenomenon, the tendency to engage in aggressive behaviour over the lifetime is relatively stable since childhood [3, 4].

The results of a European survey demonstrated that for many bipolar and schizophrenia patients, feeling agitated is a common occurrence, particularly at mild to moderate severity levels, with patients reporting a mean of 22.4 episodes of mild agitation per year and 15.4 moderate episodes [5]. The experience of agitation was associated with internal feelings (e.g. feeling tense, restless and uneasy) more commonly than more overt behaviours such as aggression. Indeed recent qualitative research with healthcare professionals described a range of three agitation states and only the most severe level included aggressive behaviour [6]. [redacted] reported that 4.6 % of psychiatric emergencies in the emergency room or inpatient settings featured agitation [7]. The results of [redacted]

demonstrated that overt irritability and psychomotor agitation were the most common manic spectrum symptoms occurring during bipolar Major Depressive Episodes (MDEs). Of the 142 intake bipolar MDEs examined in this paper, 57.0 % were characterized by clinically significant overt expressions of irritability/anger, and 39.4 % had clinically significant psychomotor agitation; 23.9 % of the intake MDEs were characterized by both overtly expressed irritability and psychomotor agitation [8].

Levomepromazine offers analgesic effects in chronic refractory pain of cancer, neuralgia and acute postoperative pain. Its use in such conditions is supported by several guidelines and clinical studies showing the beneficial effects of levomepromazine in comparison to other antipsychotic agents.

2.5.1.3 SCIENTIFIC BACKGROUND

The current Application is submitted under Article 10.3 of Directive 2001/83/EC, i.e. hybrid. A full justification on the Legal basis of the present application is provided in Module 1.5.2.

For the purpose of this application, the reference product is Neurocil Tropfen, 40 mg/ml, Tropfen zum Einnehmen, Lösung which was licensed to Desitin Arzneimittel GMBH (6070006.00.00) on the 31st of January 2005. The suitability of the reference product has been confirmed by the German authorities [9].

The proposed indications, dosage and adverse events of the product under assessment are the same as the reference product:

- the suppression of psychomotor restlessness and agitation within the context of psychotic disorders
- acute agitation states in manic episodes
- as an adjunct therapy for the treatment of severe and/or chronic pain

The proposed product is in the form of oral solution at the concentration of 5 mg/ml. The full justification of the current application is presented in Module 1.5.2.

The registration strategy, the suitability of the reference product and various aspects of product development, have been discussed with the MHRA in a Scientific Advice meeting [10].

2.5.1.4 CLINICAL DEVELOPMENT PROGRAMME

The current clinical evaluation is based on the applicable European Guidelines for the evaluation of generic products.

According to the NtA and the EMA Q&A on Generic Products, the non-clinical and clinical overviews should particularly focus on the following elements:

- A summary of impurities present in batches of the active substance(s) (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed;
- An evaluation of the bioequivalence studies or a justification why studies were not performed with respect to the Guideline on The Investigation of Bioequivalence
- An update of published literature relevant to the substance and the present application. It may be acceptable for articles in 'peer review' journals to be annotated for this purpose.

- Every claim in the summary of product characteristics (SmPC) not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non-clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.
- When different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance of the reference medicinal product are used, additional information providing proof that their safety and/or efficacy profile is not different from the one of the reference medicinal product should be submitted.
- For a hybrid of a reference medicinal product (Art 10.3) it is not required to provide the results of toxicological and pharmacological tests or the results of clinical trials. The results of the bioequivalence studies performed where appropriate should be included in section 5.3.1.

Non-clinical and clinical summaries are only mandatory if new additional studies have been provided within the documentation.

The full literature articles used during the compilation of the Clinical Overview are provided in Module 5.

2.5.1.5 SEARCH STRATEGY

This Clinical Overview examines the current state of published scientific knowledge available on the clinical properties and the established clinical use of the active substance aimed to justify the pharmacological and medical rationale for the proposed product and for the intended therapeutic indication.

In order to compile the Clinical overview, a literature review was conducted aiming to properly describe the relevant aspects regarding the pharmacology, pharmacokinetics, efficacy and safety of the product in humans. This literature search has demonstrated that a broad experience exists on the clinical use of the active substance for the specific indication. A survey of the pharmacological properties of the drug is provided, as well as a detailed discussion on its efficacy and safety together with its overall place in current clinical practice.

The search was performed within the biomedical databases, mostly, but not exclusively, in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Cochrane Central Register of Controlled Trials (CENTRAL) (https://www.cochranelibrary.com/central). PubMed comprises more than 30 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites. Pre- and post-marketing studies were taken into account and special emphasis was put to include published literature concerning experience in the form of epidemiological studies and meta-analysis where available. CENTRAL is a highly concentrated source of reports of randomized and quasi-randomized controlled trials. Most CENTRAL records are taken from bibliographic databases (mainly PubMed and Embase), but records are also derived from other published and unpublished sources, including ClinicalTrials.gov and the WHO's International Clinical Trials Registry Platform.

For toxicological information, the various TOXNET databases were used, such as:

- HSDB (https://pubchem.ncbi.nlm.nih.gov/)
- LactMed (https://www.ncbi.nlm.nih.gov/books/NBK501922/)
- ChemIDPlus (https://chem.nlm.nih.gov/chemidplus/)

- LiverTox (https://www.ncbi.nlm.nih.gov/books/NBK547852/)

Search results were supported by searching additional web search engines, such as Google and Google Scholar. In addition, the databases listed in Table I have also been used to complement the search. Both favourable and unfavourable documentation is being presented.

For the Clinical overview the search terms included the keywords "levomepromazine" or "methotrimeprazine" coupled with "pharmacology", "pharmacodynamics", "pharmacokinetics", "toxicity" or "toxicology" and the results were limited to "humans". In a second round, more specific keywords were searched in relation to the above-mentioned drug. Alternatively, review works were considered to identify other potentially relevant studies. In March 2021 the search term "levomepromazine" limited "humans" yielded about 683 results in the PubMed database. Since levomepromazine has a well-established medicinal use, a number of representative articles was selected to compile this report.

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

2.5.2.1 BIOEQUIVALENCE STUDY

A bioequivalence study has not been performed to support the application, since the test and reference products are oral solutions at the time of administration and levomepromazine is a BCS I active substance. Although the test and reference product are presented in different concentrations and contain different excipients, these differences are not expected to affect wither the rate or the extent of levomepromazine's absorption, as discussed in the following sections.

1. ***Oral solution at the time of administration***

According to the EMA Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**, 2010), Appendix II it is stated for oral solutions:

> *"If the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived. However if the excipients may affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect transport proteins), in vivo solubility (e.g. co-solvents) or in vivo stability of the active substance, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data. The same requirements for similarity in excipients apply for oral solutions as for Biowaivers".*

The EMA Questions and Answers on Clinical pharmacology and pharmacokinetics (Sections 6.2-6.3) further elaborate on the issue. Conceptually, bioequivalence investigates whether two products exhibit comparable *in vivo* release from the formulation and therefore they exhibit similar bioavailability. Consequently, oral solutions may be considered less critical particularly in the case of aqueous solutions containing completely solubilized active substances, because neither the manufacturing process nor the formulation affects drug release and the formulation impact on absorption should be minimal. However, excipients might impact the bioavailability in different, not necessarily foreseeable ways, since systematic investigations of specific excipients are rarely available

and in general, *in vivo* susceptibility of active substances towards excipient effects seems to be different.

2. BCS I active substance

Levomepromazine hydrochloride is a highly soluble and highly permeable active substance and therefore can be classified as BCS I active substance. Levomepromazine hydrochloride is reported as freely soluble and has been classified as highly permeable [11].

The equilibrium solubility of levomepromazine hydrochloride throughout the physiological pH range was measured by using the saturation shake-flask method. The results classify levomepromazine hydrochloride as highly soluble. The results of the study are presented in Module 3.2.P.2.

The low oral bioavailability (21-53 %) is attributed to the extensive first pass metabolism of the active substance.

For BCS I, absorption is very unlikely to be affected by excipient changes. Only a limited number of potentially critical excipients have been identified which are relevant to BCS Class I and III compounds [12]:

- Excipients that can influence intestinal transit (i.e. osmotically active alcohol sugars)
- Surfactants that can alter permeability (through passive mechanisms or effects on transport proteins)

A discussion on the impact of excipients is presented in the following section.

3. Negligible impact of excipients

The EMA Guideline specifically indicates certain 'critical excipients' known to potentially affect *in vivo* bioavailability, by means of *in vitro* and/or *in vivo* interactions. In addition, the last sentence including the reference to Appendix III (Section IV.2) defines that similarity of excipients should be handled according to requirements specified for Biopharmaceutics Classification System (BCS)-based biowaivers. Consequently, differences in excipients could be handled more flexible with BCS class I drug substances (composition similarity is not mandatory), but qualitative similarity and very close quantitative similarity of excipients is expected in the case of BCS class III drug substances. This is considered justified because the scientific rationale regarding the potential interaction between highly soluble drug substances (BCS class I or III) and excipients, likewise applies to drug substances already in solution and immediate release formulations (rapid or very rapid *in vitro* dissolution). Although the impact of excipients in immediate release dosage forms on bioavailability of highly soluble and completely absorbable drug substances (i.e., BCS class I) is considered rather unlikely it cannot be completely excluded.

[redacted]

[redacted] The reference product is presented as oral drops of 40 mg/ml concentration, while the test product is administered as oral solution with 25 mg/5 ml concentration.

For BCS I active substance the [redacted] is considered rather unlikely, since the active substances are already highly soluble. Ethanol, glycerol or propylene glycol do not affect gastrointestinal transit time or alter permeability.

Moreover, the reference product is administered either undiluted or diluted in an unspecified amount of water. Therefore, concentration differences in either the active substance [redacted] are considered rather unlikely.

The quantitative differences of the product under assessment and the reference product are presented in the Appendix I of the present document along with a detailed discussion on each excipient of the test and reference products.

4. Low risk associated with inequivalence

Since levomepromazine hydrochloride is considered highly soluble and is administered as an oral solution, it is reasonable to expect that it will not cause any bioavailability problems. In principal, bioinequivalence could also be caused by a difference in GI absorption, resulting from differences in composition between the test formulation and the reference formulation with respect to the excipients. None of the excipients of the formulation have a known impact on the rate or the extent of levomepromazine absorption and none has any known effect on the gastrointestinal transit time.

Four possible situations could be envisaged resulting from a false biowaiver decision that is declaring a test formulation bioequivalent to the reference formulation, whereas this test formulation would be declared bioinequivalent when subjected to an *in vivo* BE study. The test formulation may give rise to a lower or to a higher AUC and/or to a lower or to a higher C_{max} than the reference product.

In the first instance, the test formulation has a lower absorption than that of the reference product and thus might be clinically less effective. This would have serious clinical consequence only in severe, life-threatening diseases that require acute treatment. However, levomepromazine is not used in life-threatening diseases. The second situation in which a false biowaiver decision would be clinically relevant is when the drug formulation is super-bioavailable, that is, the test formulation has a higher AUC and C_{max} than the reference. However, serious side effects with levomepromazine have been observed at exceptionally high doses and serum levels.

Furthermore, levomepromazine is not classified as a Narrow Therapeutic Index Drug which would exclude it from biowaiving according to the EMA regulation. Therapeutic levels of levomepromazine are achieved at serum concentrations between 0.02 mg/L and 0.14 mg/L ([13] as reported in [1], [14]). In the same case report, the fatal blood drug concentration recorded was 4.1 mg/L and the major metabolites desmethyl-methotrimeprazine and methotrimeprazine sulfoxide were also measured at 2.0 and 1.8 mg/L, respectively ([13] as reported in [1], [14]). The ratio of toxic to therapeutic concentrations is very high and levomepromazine is therefore not classified as a NTI.

In summary:

- Levomepromazine 25 mg/5 ml oral solution is a hybrid form of the reference product Neurocil Tropfen, 40 mg/ml of Desitin Arzneimittel GMBH since both products have the same

qualitative composition in the active substance levomepromazine, in the same pharmaceutical dosage form of an oral solution at time of administration. The concentration of the two formulations is different, however the administered amount of levomepromazine is the same as described in the proposed SmPC. Although a difference in excipients exist between the proposed formulation and the reference product, any effect on the gastrointestinal transit is not expected.

- Levomepromazine hydrochloride is a BCS I active substance, i.e. it is a high solubility, high permeability compound. BCS Class I active substances are eligible for a biowaiver.
- The proposed product Levomepromazine 25 mg/5 ml oral solution contains the [redacted] excipients propylene glycol and glycerol. However, as discussed previously, the amount of these excipients are not expected to affect gastrointestinal transit, absorption, *in vivo* solubility or *in vivo* stability of the active substance.
- The risk of bioinequivalence is negligible.

2.5.2.2 DOSAGE FORM/STRENGTH PROPORTIONALITY

Levomepromazine oral solution is available at 25 mg/5 ml strength.

2.5.2.3 DIFFERENCES BETWEEN THE TO-BE-MARKETED FORMULATION AND THE FORMULATION(S) USED IN CLINICAL TRIALS

Clinical studies have not been performed with the proposed formulation.

2.5.2.4 INFLUENCE OF FOOD ON EXPOSURE

No food effect has been observed in immediate-release dosage forms containing Levomepromazine.

2.5.2.5 INFLUENCE OF METHOD OF ADMINISTRATION

The proposed product is intended to be administered orally as oral solution.

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

2.5.3.1 PHARMACOKINETICS

The pharmacokinetic data of levomepromazine are summarized in Table II.

Table II Pharmacokinetic data of Levomepromazine

PK Data	Reported Values
Bioavailability	50 % [1, 15, 16] 40 % [17] 21 % [18] (53 % Fraction absorbed)
Onset of Action	30 min [15, 16]
Time to Maximum Serum Concentration (T_{max})	2-3 h [19] 1-3 h [1, 15, 16] 1-6 h [20]
Half-life ($t_{1/2}$)	30 h [21] 15-30 h [1, 15, 16] [17][1] Mean: 32.9 h, Range: 16.5-77.8 h [19][2] 8.9-34.7 h [20]
Duration of Action	12-24 h [15, 16]
VD_{ss} (Volume of distribution at steady state)	12 L/kg [18, 21]
CL_t (Total Clearance)	9.9 mL/min/kg [18, 21]
CL_r (Renal Clearance)	3.96 mL/min/kg [18]
CL_h (Hepatic Clearance)	5.94 mL/min/kg [18]
[1]*According to* [redacted] *[22] this is the half-life for biological effects* [2]*According to* [redacted] *[22] this is the terminal half-life*	

2.5.3.1.1 Absorption

Therapeutic levels of levomepromazine are achieved at serum concentrations between 0.02 mg/L and 0.14 mg/L [1]. Plasma concentrations of levomepromazine reach their maximum levels 30 min-90 min after intramuscular injection, and 1 h–3 h after oral administration.

[redacted] has reported on single and multiple oral and intramuscular modes of application of levomepromazine to patients that the absolute bioavailability (single oral versus single intramuscular administration) ranged from 33-74 % (mean 53 %) and that the systemic bioavailability is low due to a substantial individually variable first pass metabolism [16, 19].

The low bioavailability with high inter-individual variation of levomepromazine was also confirmed in the study of [redacted] In this study, the pharmacokinetics of levomepromazine after a single oral administration and intravenous infusion of 100 mg levomepromazine were investigated and the two oral formulations (oblong and coated levomepromazine tablets) were bioequivalent (Table III).

Table III Pharmacokinetic parameters and administration of 100 mg levomepromazine to healthy volunteers [20]

Route of administration	Oral (n=12)		Intravenous infusion (n=6)
Formulation	Oblong tablet (levomepromazine maleate) Geometric mean (C.V.) (range)	Coated tablet (levomepromazine maleate) Geometric mean (C.V.) (range)	Solution (levomepromazine hydrochloride) Geometric mean (C.V.) (range)
AUC* (ng × h/ml)	355.2 (57.3) (189 - 1,025)	372.3 (79.6) (123 -1.314)	2,169 (21.7) (1574 - 3.781)
C_{max}* (ng/ml)	46.2 (58.1) (19.1 - 103.9)	49.2 (51.5) (24.0 - 107.0)	406.6 (18.5) (310.2 - 578.4)
MRT (h)	16.8 (29.6) (7.1 -48.3)	14.5 (29.8) (7.7 - 26.0)	20.8 (17.5) (23.6 - 39.8)
$t_{1/2}$ (h)	19.4 (49.4) (11.5 - 34.7)	14.2 (37.2) (8.9 - 27.0)	29.8 (12.5) (15.8- 34.0)
T_{max} (h)	Arithmetic mean (C.V.) range		
	2.2 (78.3) (1.0 - 6.0)	1.9 (60.8) (1.0 - 5.0)	0.83 (15.5) (0.75 - 1.0)

**These values were dose-adjusted with respect to the free levomepromazine base by the following ratios: the molecular weight of levomepromazine hydrochloride/molecular weight of levomepromazine base or the molecular weight of levomepromazine maleate/molecular weight of levomepromazine base*

2.5.3.1.2 Distribution

The volume of distribution of Levomepromazine was calculated by [redacted] after single and multiple doses in human. The apparent volume of distribution (V_β) was 23 to 42 L/kg body weight, and the biological half-life, 15 to 30 hr [16].

Plasma levels of levomepromazine under standard psychiatric therapy range between 15 ng/ml and 156 ng/ml [19].

Levomepromazine crosses the BBB and the regional distribution in human brain tissue is presented in Figure 2.

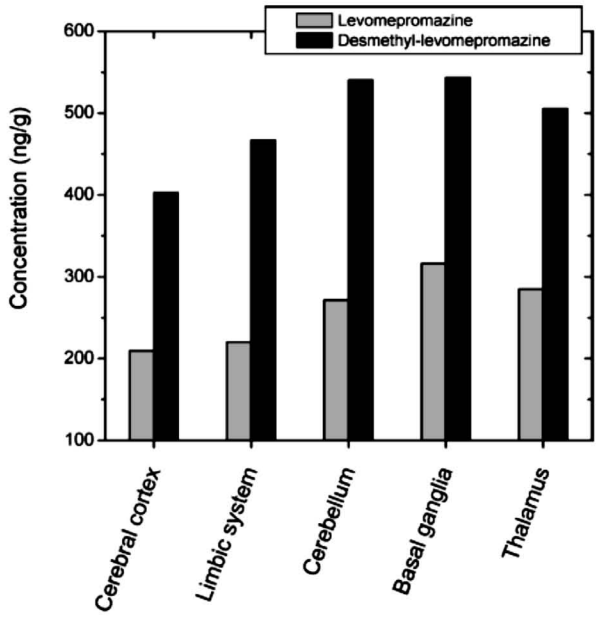

Figure 2 Regional distribution of levomepromazine and desmethyl-levomepromazine in human brain tissue [23]

Levomepromazine (phenothiazines) is highly bound to plasma proteins. Phenothiazines readily cross the placenta. It is not known if the drugs are distributed into milk; however, the size of the molecules and their ability to readily cross the blood-brain barrier suggest that the drugs would be distributed into milk [24].

2.5.3.1.3 Metabolism and Excretion

Levomepromazine is extensively metabolized in the body before being excreted. Two metabolic routes S-oxidation and N-demethylation, were reported to be the dominant biotransformation pathways of levomepromazine in humans [25, 26]. N-desmethyl-levomepromazine, the N-demethylated metabolite, showed an almost equally potent receptor binding activity (dopaminergic and a_1-adrenergic) as did the parent drug, whereas the 5-sulfoxide was considerably less active in this respect.

Pharmacokinetic studies with levomepromazine have shown that patients generally have 1-2 times higher plasma concentrations of levomepromazine sulfoxide than of levomepromazine itself after repeated oral doses of the drug [16, 19, 27]. N-Monodesmethyl levomepromazine has also been identified in plasma from patients [27]. The plasma concentrations of this metabolite have been measured in five psychiatric patients who were treated with levomepromazine tablets. The plasma levels of monodesmethyl levomepromazine were about twice as high as the levels of the parent drug in four of the patients, and about 50% of the levomepromazine concentration in the fifth patient [28].

2.5 Clinical overview

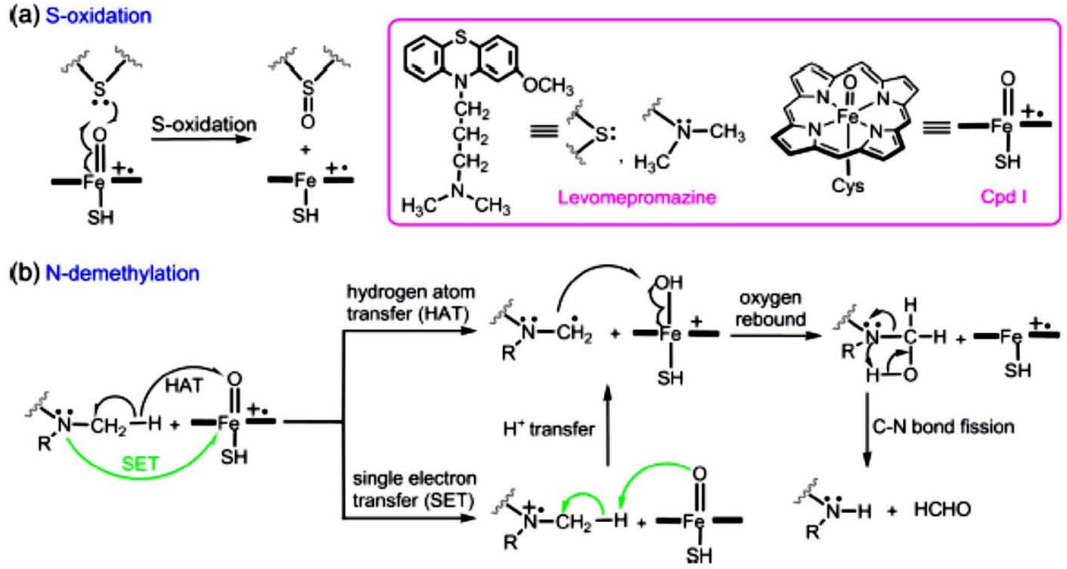

Figure 3 Metabolic mechanisms of Levomepromazine catalysed by cytochrome P450 [29]

Cytochrome P450 is potentially responsible for the metabolism of levomepromazine. The experimental work performed *in vitro* using cDNA expressed human CYP isoforms has indicated that CYP3A4 is the main isoform responsible for S-oxidation (72 %) and N-demethylation (78 %) at a therapeutic concentration of LM (10 mM), while CYP1A2 contributes to a lesser degree to S-oxidation (20 %) [30]. It can be negligible (0.1 - 8 %) for CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 in catalyzing the above-mentioned reactions.

The variation in the metabolism of most tricyclic antidepressants and antipsychotics appears to be associated with the genetic polymorphism of the debrisoquin hydroxylation, which is catalysed by the P450 isoenzymeCYP2D6 [31]. Levomepromazine, as other antipsychotic agents, is a competitive inhibitor of CYP2D6. This was demonstrated *in vitro* with liver microsomes as well as *in vivo* in humans [31-34]. The study of [redacted] demonstrated that levomepromazine's disposition does not co-vary with the polymorphic debrisoquin hydroxylation [20]. This implies that CYP2D6 contributes little to the total clearance of levomepromazine and has a negligible effect on its serum concentration. Although levomepromazine may be not metabolized to a major extent by CYP2D6, it is a potent inhibitor of oxidative metabolism of the neuroleptics or tricyclic antidepressants [33, 35, 36].

In the study of [redacted] a single 50 or 100 mg dose of levomepromazine was given to healthy male volunteers and urine samples were collected for 24 hours. The following figure shows the chemical structures of levomepromazine and those of its metabolites that have been identified [25, 26, 37, 38].

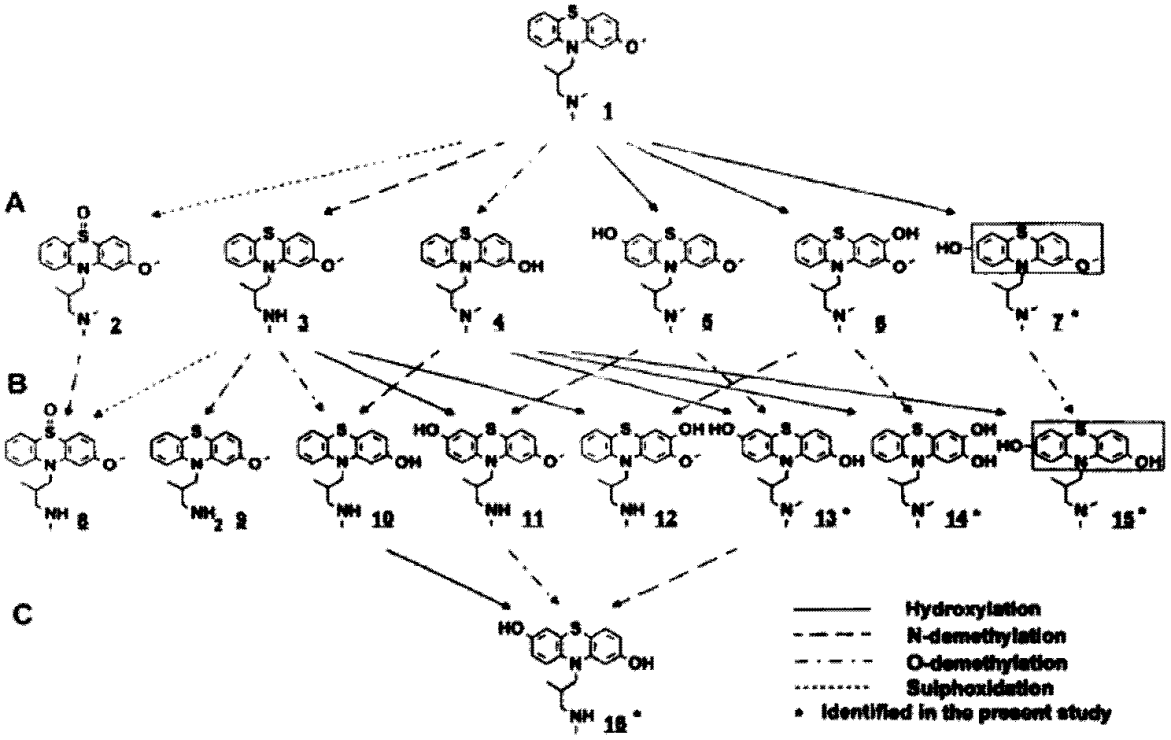

*Figure 4 Structure of LM (1) and metabolites. Metabolites identified in the present investigation are marked with an asterisk. **A**: Metabolites formed by one metabolic step; **B**: Metabolites formed by two metabolic steps; **C**: Metabolite formed by three metabolic steps. 2 =LM sulphoxide; 3 =N-desmethyl LM; 4 =O-desmethyl LM; 5 =7-hydroxy LM; 6 =3-hydroxyLM; 7 = 'ring-hydroxy LM'; 8 = N-desmethyl LM sulphoxide; 9 = N-didesmethyl LM; 10 = N,O-didesmethyl LM; 11 = N-desmethyl 7-hydroxy LM; 12 = N-desmethyl 3-hydroxy LM; 13 = O-desmethyl 7-hydroxy LM; 14 = O-desmethyl 3-hydroxy LM; 15=O-desmethyl 'ring-hydroxy LM'; 16 = N,O-didesmethyl 7-hydroxy LM. Conjugates of the metabolites containing hydroxyl groups are not indicated [26]*

The total serum clearance has been reported to be 48 ± 14 L/min [20].

The biological half-lives for levomepromazine were similar to those previously reported for chlorpromazine [39]. With half-lives ranging from 15 to 30 hours, one would estimate that steady-state was reached after 3 to 5 days of maintenance dosing with levomepromazine [16]. The same author reported a biological half-life of levomepromazine ranging from 16.5 hours to 77.8 hours after administration of tablets and syrup [19].

2.5.3.1.4 Dose proportionality

After an extensive literature search, studies reporting the area under the plasma concentration for various doses of levomepromazine after single administration are not available in the public domain.

[redacted][19] studied the pharmacokinetics and relative bioavailability of levomepromazine after repeated administration of tablets and syrup. Daily doses of 50-350 mg were administered in 8 patients. Measurements were performed at the steady state during one dosage interval and no clear correlation between the administered dose and the area under the curve can be established, due to the high intersubject variability of the active substance and the heterogeneity of the subjects. For

example, the highest AUC/dose ratio was observed in a 80 year old patient, due to the very slow elimination of the active substance (2-3 fold longer half-life), possibly due to reduced renal function.

[redacted] [40] performed a pharmacokinetic analysis using a one-compartment model for levomepromazine. The model revealed that the apparent volume of distribution was 4.1 ± 2.4 L/kg and the metabolic clearance was 309 ± 225 L/h/70 kg. The authors used mean doses ranging from 1.2 to 3.86 mg/h (approximately 25-100 mg/day). Levomepromazine was administered as intravenous continuous infusion. The main pharmacokinetic parameters did not show dose-dependency. The results of the study should be interpreted with caution, given the different behaviour between oral and intravenous levomepromazine.

[redacted] [20] determined an absolute bioavailability of 21 %, which is quite different from the 53 % calculated by [redacted] [16] after single oral and intramuscular administration of levomepromazine. [redacted] used a 100 mg dose, while [redacted] used a 25 mg dose. Although the bioavailability measured by [redacted] is not absolute, since levomepromazine was administered intramuscularly rather than intravenously, this difference may be an indication of a nonlinearity at the dose range 25-100 mg, since higher doses showed lower bioavailability.

2.5.3.1.5 Pharmacokinetics Related to Intrinsic Factors

2.5.3.1.5.1 *Age*

The age of subjects included in the study of [redacted] was ranging from 37 to 80 years and significant differences were identified in the pharmacokinetics of levomepromazine [19].

2.5.3.1.5.2 *Sex*

The pharmacokinetic parameters of levomepromazine are not affected by sex as demonstrated in the study of [redacted] [19].

2.5.3.1.5.3 *Race*

The racial effects on levomepromazine pharmacokinetics have not been reported. However, differences in clearance of perphenazine have been reported and attributed to racial differences in CYP2D6 polymorphism frequencies between African Americans and others [41].

2.5.3.1.5.4 *Weight*

The weight of subjects included in the study of [redacted] was ranging from 62 to 96 kg and significant differences were identified in the pharmacokinetics of levomepromazine [19].

2.5.3.1.5.5 *Renal Impairment*

Studies evaluating the pharmacokinetics of levomepromazine in renal impaired patients are not available in the public domain. The renal drug handbook recommends doses of levomepromazine as in normal renal function in conditions of GFR being 20-50 ml/min or 10-20 ml/min and initial smaller doses of levomepromazine when GFR is < 10 ml/min [42].

2.5.3.1.5.6 *Hepatic Impairment*

It is considered that hepatic dysfunction increases the bioavailability of chlorpromazine and delays its elimination [43], however, studies evaluating the pharmacokinetics of levomepromazine in patients with hepatic dysfunction are not available in the public domain.

2.5.3.1.6 Pharmacokinetics Related to Extrinsic Factors

2.5.3.1.6.1 *Smoking*

The pharmacokinetics of smoking and non-smoking subjects after administration of levomepromazine have not been studied. The effects of smoking on pharmacokinetic parameters have been reported for other phenothiazines, such as perphenazine. [redacted] demonstrated active smokers eliminated perphenazine 159 L/h faster than non-smokers in each race studied [41].

2.5.3.1.6.2 *Diet*

Food effects on levomepromazine pharmacokinetics have not been reported.

2.5.3.1.7 Pharmacokinetic Studies in Special Population

2.5.3.1.7.1 *Paediatrics*

Data concerning the effect of age on levomepromazine pharmacokinetics are not available.

2.5.3.1.7.2 *Geriatrics*

Pharmacokinetic studies of levomepromazine have not been performed in geriatric populations. In the study of [redacted] the pharmacokinetic parameters of one subject aged 80 years did not differ significantly from the patients aged 37-61 years [19].

2.5.3.1.8 Pharmacokinetic Drug Interactions

2.5.3.1.8.1 *Effects of other medicinal products on levomepromazine*

Concomitant administration of carbamazepine and barbiturates can induce the CYP enzyme activity resulting in decreased levomepromazine plasma concentrations [44].

Concomitant administration of drugs known to inhibit hepatic metabolism of levomepromazine, might lead to enhanced therapeutic effects of levomepromazine [45].

2.5.3.1.8.2 *Effects of levomepromazine on other medicinal products*

Levomepromazine is an inhibitor of cytochrome P450 2D6 (CYP2D6). Co-administration of levomepromazine and drugs primarily metabolised by the CYP2D6 enzyme system may result in increased plasma concentrations of these drugs (risperidone, haloperidol, amitriptyline, captopril, ondansetron, codeine, celecoxib, flecainide and amphetamine derivatives) [45].

Concomitant use of levomepromazine may affect the metabolism of phenytoin, resulting in toxic plasma concentrations of phenytoin [46].

Levomepromazine can affect the hepatic metabolism of TCAs resulting in increased plasma levels of TCAs. Caution should be exercised if levomepromazine is combined with MAO inhibitors [47].

2.5.3.1.8.3 *Other drug interactions*

The combined use of levomepromazine and propranolol may result to increased levels of both drugs [48]. The absorption of other drug substances can be affected by the inhibition of gastrointestinal motility.

2.5.3.2 PHARMACODYNAMICS

2.5.3.2.1 Mechanism of Action

Levomepromazine belongs to the group of phenothiazines. Though exact mechanism of action has to be determined, levomepromazine antagonizes dopamine receptors in the central nervous system, depressing the cerebral cortex, hypothalamus and limbic system. The clinical effects produced by this action include: a depressant action on conditioned responses and emotional responsiveness; a sedative action useful for the treatment of restlessness and confusion; an anti-emetic effect through blockade of the chemoreceptor trigger zone (CTZ), which is useful to treat vomiting; and antihistamine activity [49, 50].

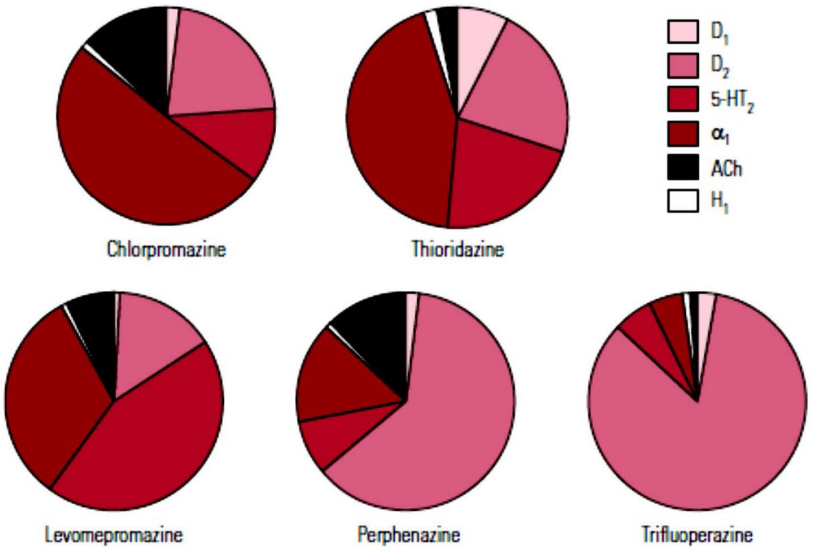

Figure 5 Receptor binding profiles of some of the phenothiazine antipsychotics, showing percentage of total binding contributed to by each transmitter type [51]

2.5.3.2.2 Primary Pharmacodynamics

Levomepromazine has a broad receptor binding profile (Figure 5) covering antagonist actions at D_1–D_4, 5-HT_1 and 5-HT_2, noradrenergic (including, unlike chlorpromazine, a_2 as well as a_1), histamine H_1, and muscarinic M_1 and M_2 sites [52].

2.5.3.2.2.1 *Anti-dopaminergic Effect*

The most important feature of phenothiazine derivatives with antipsychotic activity is that they non-selectively inhibit all the five types of dopamine receptors. Their most important effect is their D_2 (and D_3) receptor-blocking activity, since it is correlated with the antipsychotic effect of the molecule [53]. The highest density of D_2 receptors in the brain is found in the striatum, nucleus accumbens, ventral tegmental area, and substantia nigra, and the therapeutic effect is due to the inhibition of D_2 receptors in neurons originating from the ventral tegmental area, and projecting to the limbic system (mesolimbic dopaminergic pathway). As a result, phenothiazine-based antipsychotics can effectively reduce the positive symptoms of schizophrenia (hallucinations, delusions, and disorganized speech and behaviour). Furthermore, dopamine receptor blockade of the medullary chemoreceptive trigger zone also results in an antiemetic effect. However, the adverse effects of the drug are also due to inhibition of D_2 receptors. The inhibition of the dopaminergic nigro-striatal system leads to a wide variety of EPS, such as akathisia, tardive dyskinesia, Parkinsonism, acute dystonic reactions, and other drug-induced dyskinesias (tic, chorea, or athetosis). The anti-dopaminergic effect on the tuberoinfundibular system causes hyperprolactinemia as a result of the termination of tonic inhibition of lactotrophic cells by dopamine. The D_2 receptor blockade is proven to be in the background of neuroleptic malignant syndrome (hyperthermia, muscle rigidity, and autonomic dysregulation), which is a potentially fatal adverse effect [50].

2.5.3.2.2.2 *Anti-histaminic Effect*

All phenothiazine derivatives used in clinical practice have an antihistamine effect, among which promethazine has the most significant one. It mainly involves inhibition of H_1 receptors, and plays a role in the alleviation of allergic symptoms [54]. In the nervous system, H_1 receptors are found mainly in the tuberomammillary nucleus. This area is responsible for multiple tasks, among which regulation of the sleep–wake cycle, appetite and body temperature are the most essential. The inhibition of the histaminergic neurons in this nucleus is responsible for the sedative effects of antihistamines and antipsychotics, and for an increased appetite, moreover subsequent hypothermia or hyperthermia may also develop through the inhibition of body temperature regulation [55].

2.5.3.2.2.3 *Anti-serotonergic Effect*

Phenothiazine antipsychotics have high affinity for serotonin (5-hydroxytryptamine, 5-HT) receptors, the most important of which is the inhibition of 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors in achieving the antipsychotic effect [56], however, it is crucial mainly in the case of atypical antipsychotics. For phenothiazine antipsychotics, the inhibition of serotonin receptors results in anxiolytic and antidepressant activity, it reduces aggression and the risk of developing EPS, but leads to weight gain, changes in blood pressure, and the development of ejaculatory disorders [57].

2.5.3.2.2.4 *Alpha-Adrenergic Receptor-Blocking Effect*

Phenothiazine type antipsychotics can inhibit both α_1 and α_2 adrenergic receptors. The inhibition of α_1 receptors is mainly responsible for the sympatholytic side-effects such as hypotension, orthostatic hypotension, reflex tachycardia, dizziness, myosis, and sexual dysfunction. The inhibition of α_2 receptors may have an antidepressant effect [57].

2.5.3.2.2.5 *Anticholinergic Effect*

Phenothiazine antipsychotics have special affinity for M_1 and M_2 muscarinic acetylcholine receptors. The inhibition of M_1 receptors can be related to the blocking activity of the autonomic ganglia, which results in autonomic symptoms, such as dry mouth, constipation, urinary retention, dry and warm skin, nausea, mydriasis, closed-angle glaucoma, nasal congestion, priapism, and orthostatic hypotension. Phenothiazines can effectively reduce sea sickness because of their central antimuscarinic effect [57].

2.5.3.2.3 Secondary Pharmacodynamics

Although other phenothiazines exhibit also additional effects, for levomepromazine only anti-microbial effects have been demonstrated. The antimicrobial effect of levomepromazine has not been established to humans and the relevant *in vitro* studies are presented in Module 2.4.

2.5.3.2.4 Genetic Differences

Influence of genetic polymorphisms on levomepromazine effects have not been studied.

2.5.3.2.5 Pharmacodynamic Drug Interactions

2.5.3.2.5.1 *Effects of other medicinal products on levomepromazine*

The effects of levomepromazine can be inhibited by anticholinergic medicinal products, such as biperiden [58].

The moderate anticholinergic effects of levomepromazine can be enhanced by other anticholinergic agents or other medicinal products with anticholinergic effects [59].

2.5.3.2.5.2 *Effects of levomepromazine on other medicinal products*

The concomitant use of levomepromazine with analgesics, hypnotic agents, sedatives or other CNS depressants can lead to increased sedation and respiratory depression [59].

Levomepromazine can enhance the respiratory depression after concomitant administration with polypeptide antibiotics (capreomycin, colistin, polymyxin B).

Patients undergoing surgical repair should be carefully monitored for potential hypotension. The dose of anaesthetics may need to be reduced [60].

The effects of antihypertensive drugs can be enhanced with the concomitant use of levomepromazine. The hypotensive effects of guanethidine, clonidine and alpha-methyldopa can, however, be depressed [59].

The combined use of levomepromazine with dopamine agonists (e.g. levodopa) may result in diminished effects of dopamine agonists [61]. The alpha-adrenergic effects of adrenaline are also diminished.

The response to gonadorelin can be diminished by phenothiazines due to the enhanced levels of prolactin [62].

2.5.3.2.5.3 *Other drug interactions*

The concomitant use of levomepromazine and piperazine anthelmintics and metoclopramide can result to an increased risk of extrapyramidal symptoms [63].

Treatment with levomepromazine may affect the PKU Test for Phenylketonuria (false-positive result) [64].

The concomitant used of medicinal products that prolong the QT interval (class IA or III antiarrhythmics, cisapride, certain antibiotics, anti-malarials, antihistamines, antidepressants) or lead to hypokalaemia (e.g. certain diuretics) should be avoided [59].

2.5.4 OVERVIEW OF EFFICACY

2.5.4.1 PSYCHOTIC DISORDERS

2.5.4.1.1 Main Studies

2.5.4.1.1.1 *Controlled Studies*

In the study of [redacted] the effects of Levomepromazine were compared to those of chlorpromazine in the treatment-resistant schizophrenia (TRS). In this study, both Levomepromazine and chlorpromazine improved TRS (treatment-resistant schizophrenia) relative to baseline. Although there was no significant difference between the 2 groups in treatment response at study end point, hierarchical linear modelling of longitudinal outcome revealed a significant (p=0.006) advantage of levomepromazine over chlorpromazine for the BPRS total score (Brief Psychiatric Rating Scale). Ten of 19 participants on levomepromazine and 8 of 19 on chlorpromazine met the criterion for treatment response, and 9 of the 18 responders did so on 200-700 mg/day phenothiazine [65].

2.5 Clinical overview

Table IV Treatment outcome [65]

Variable	Levomepromazine (n = 19)	Chlorpromazine (n = 19)
Completed HAL phase, 60 mg/d × 4 week	12	13
Advanced after HAL, 60 mg/d × 1 - 3 week‡	6	2
Advanced after HAL, < 60 mg/d‡	1	4
Randomization phase completed	17	14
Premature withdrawal	2	5
Mean baseline neuroleptic dose (and SD), mg/d§	1611 (879) (n = 19)	1872 (1333) (n = 19)
Mean final neuroleptic dose (and SD), mg/d	813 (225)	762 (199)
p value	< 0.001	< 0.002
Mean baseline neuroleptic dose (and SD), mg/d (completers)§	1624 (914) (n = 17)	1623 (856) (n = 14)
Mean final neuroleptic dose (and SD), mg/d (completers)	799 (234)	763 (215)
p value	< 0.001	< 0.005
BPRS total decrease ≥ 25 %	10	8
Criteria of Kane et al [66] for response	6	4
PANSS (total) decrease ≥ 25 %	11	6**
Mean baseline neuroleptic dose of responders (and SD), mg/d§	1715 (966) (n = 10)	1763 (921) (n = 8)
Mean final neuroleptic dose of responders (and SD), mg/d††	710 (265)	722 (272)
p value	< 0.005	0.026
Mean weight at baseline (and SD), kg	71.5 (12.2) (n = 17)	70.5 (20.2) (n = 12)
Mean weight at week 30 (and SD), kg	75.6 (12.9)	75.4 (18.4)
p value	0.046	0.015
Mean baseline QTc interval (and SD)	0.446 (0.053) (n = 11)	0.424 (0.025) (n = 12)
Mean QTc interval at week 30 (and SD)	0.429 (0.025)	0.437 (0.024)
p value	0.29	0.12

BPRS = Brief Psychiatric Rating Scale; HAL = haloperidol; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation
**None of the between-group comparisons are significantly different*
†Unless otherwise indicated
‡Subjects advanced to randomized phase without reaching HAL, 60 mg/d × 4 week
§Chlorpromazine equivalents
¶Within-group comparisons
***Two additional subjects improved 21 % and 24 %, respectively*
††Subjects showing a ≥ 25 % reduction in total BPRS

A comparative investigation of the clinical efficacy and safety of intramuscular (IM) olanzapine, IM haloperidol, and IM levomepromazine in acute agitated patients with schizophrenia has been performed by [redacted] [67]. The results of the study are presented in Table V.

Table V Efficacy data of Levomepromazine [67]

IM Levomepromazine group (n = 37)			
	Baseline	Change from baseline to after 2 h	p-value vs IM Olanzapine
	Mean ± SD	Mean ± SD	
ACES PANSS	2.4 ± 0.6	1.2 ± 0.7*	0.884
Total	104.2 ± 13.7	-5.3 ± 2.4*	0.002
Positive	24.5 ± 2.9	-2.7 ± 1.2*	0.003
Negative	2.86 ± 5.2	-	-
General psychopathology	48.7 ± 6.4	-2.7 ± 1.3*	0.01
PANSS-EC	18.2 ± 2.6	-5.1 ± 2.1*	0.27
AIMS total score	7.4 ± 5.0	0.0 ± 0.0**	0.42
BARS total score	1.3 ± 1.9	0.3 ± 1.2	0.004
DIEPSS total score	7.3 ± 3.5	0.2 ± 0.6**	0.03
Pulse rate	81.1 ± 14.4	-2.9 ± 12.3	0.018
Systolic blood pressure (mmHg)	124.7 ± 16.8	-1.8 ± 14.9	0.997
Diastolic blood pressure (mmHg)	77.6 ± 11.2	1.7 ± 14.4	0.320
Glucose (mg/dL)	102.7 ± 22.0	-8.9 ± 13.5 *	0.996
*ACES, Agitation–Calmness Evaluation Scale; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, Positive and Negative Syndrome Scale Excited Component; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale; IM, intramuscular. *p<0.005 versus baseline, **p<0.005 versus IM haloperidol*			

Levomepromazine has stronger serotonin (5-HT_2A) receptor blocking effects as compared with haloperidol. The results of this study suggest that from its pharmacological profile, IM Levomepromazine is equivalent to IM olanzapine, and significantly superior to IM haloperidol, in improving poor impulse and excitement [67].

The comparative study of [redacted] supports the usefulness of levomepromazine as an adjunct for the treatment of agitated patients with acute exacerbation of schizophrenia, which has already been experienced in clinical practice. The reduction in the agitation score was greater for the combined therapy group than for the monotherapy groups of levomepromazine or haloperidol [68].

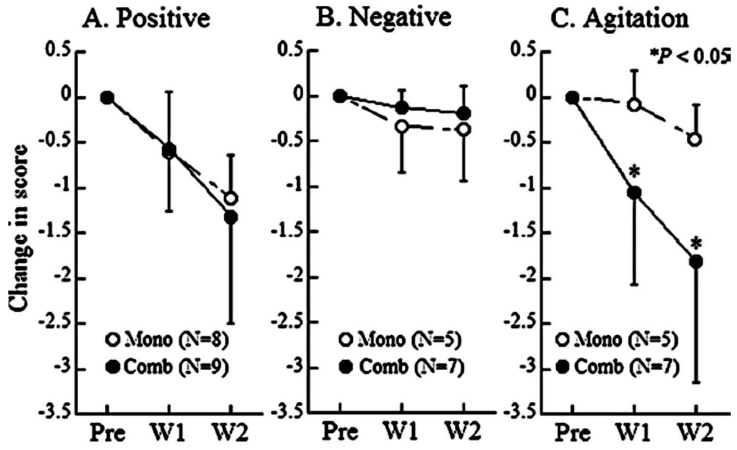

Figure 6 Changes in symptom scores for the monotherapy (Mono) compared with the combined therapy (Comb). Changes from the pre-treatment baseline score (Pre) were calculated at post-treatment Weeks 1 (W1) and 2 (W2) [68]

2.5.4.1.1.2 *Open Studies*

Levomepromazine improved 16 of 23 chronic treatment-resistant schizophrenic patients who were hospitalized in most cases for at least 2 years and who manifested positive symptoms, irritability and, in many cases, restlessness, hostility, uncooperativeness, poor concentration and aggressive behaviour. Improvement led to discharge in 7 (6 to a foster home), placement on a waiting list for a foster home in 4 and improved behaviour and autonomy in 5 patients. Five subjects developed seizures and 1 agranulocytosis [69].

2.5.4.1.1.3 *Meta-Analyses*

The most recent meta-analysis of [redacted] used placebo-controlled and head-to-head randomised controlled trials and compared 32 antipsychotics employing patients with schizophrenia or related disorders. The primary outcome was the change in overall symptoms measured with standardised rating scales. Effect size estimates suggested all antipsychotics reduced overall symptoms more than placebo (although not statistically significant for six drugs), with standardised mean differences ranging from -0.89 (95 % CrI -1.08 to -0.71) for clozapine to -0.03 (-0.59 to 0.52) for levomepromazine (40,815 participants) [70].

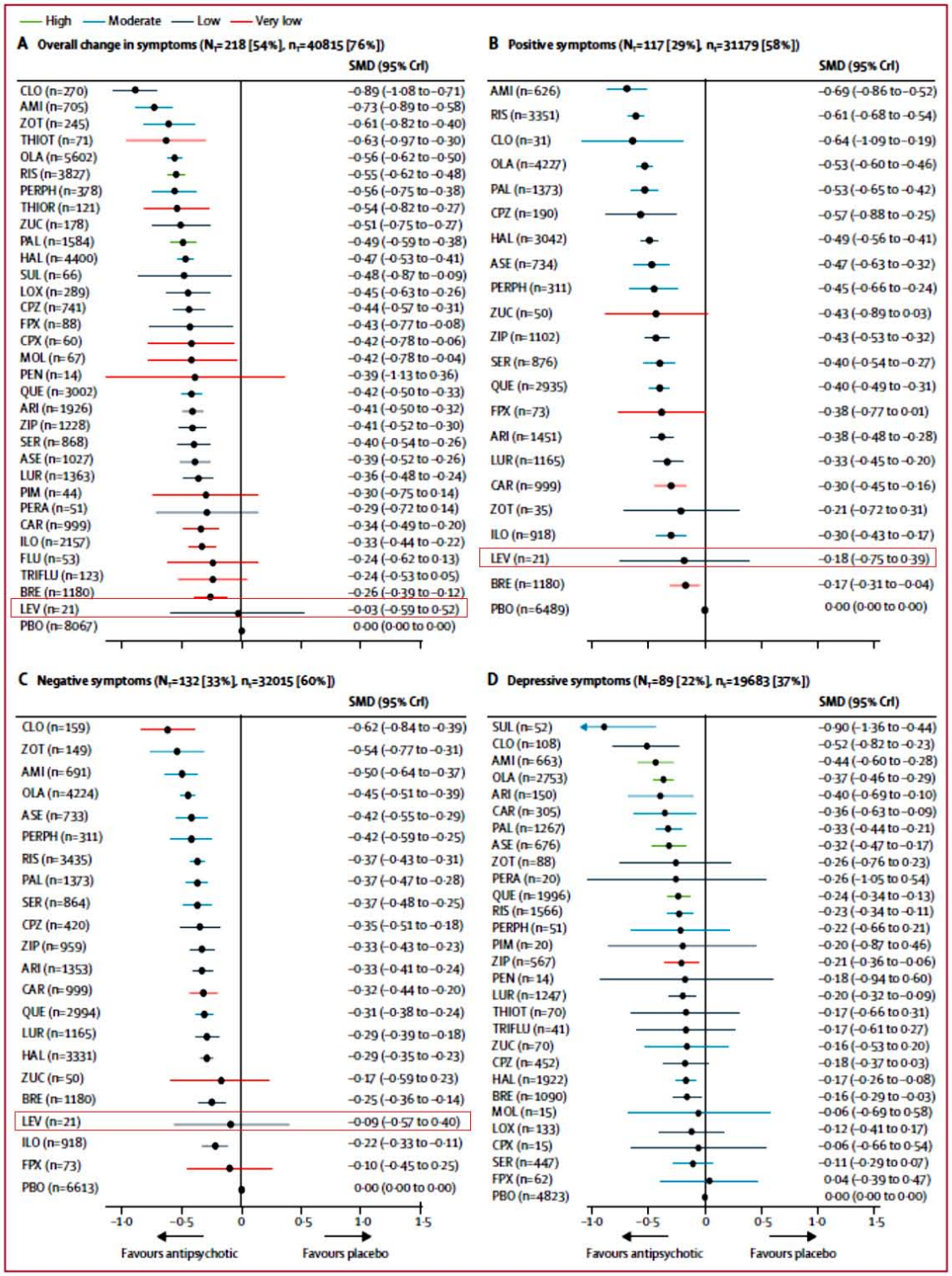

Figure 7 Change in efficacy outcomes. (A) Overall change in symptoms; (B) Positive symptoms; (C) Negative symptoms; (D) Depressive symptoms [70]

2.5 Clinical overview

The clinical effects of Levomepromazine compared to placebo or antipsychotic medications for schizophrenia and schizophreniform psychoses have been recently reviewed and reported in the meta-analysis of [redacted] [71].

Randomized controlled trials were included with 192 participants in total. For the primary outcome of leaving the study early, Levomepromazine was not significantly different compared with other antipsychotics.

The Levomepromazine arm was significantly better on Clinical Global Impression (CGI) severity compared with chlorpromazine (n = 38, 1 RCT, WMD: -0.80 CI: -1.51 to -0.09) (Figure 8).

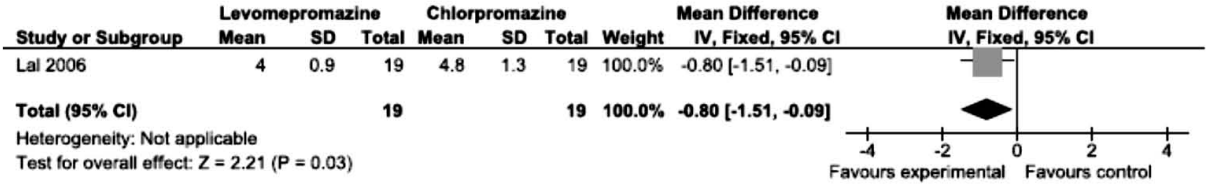

Figure 8 Global effect: CGI severity (high = poor) – long term [71]

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The effects of Levomepromazine in comparison to other typical and atypical antipsychotic medications for people with schizophrenia and schizophrenia-like disorders were recently reviewed and reported in the meta-analysis of [redacted] [72]. In the meta-analysis subjects with schizophrenia and other types of schizophrenia-like psychoses were included in randomized clinical trials [72]. The review included RCTs with 192 participants. For our primary outcome of leaving the study early, Levomepromazine was not significantly different compared with other antipsychotics. The Levomepromazine arm was significantly better on CGI severity compared with chlorpromazine (n = 38, 1 RCT, WMD -0.80 CI -1.51 to -0.09). Risperidone was better for CGI endpoint scores (n = 42, 1 RCT, RR 2.33 CI 1.11 to 4.89, NNT 3 CI 2 to 10) compared with Levomepromazine. Recipients given Levomepromazine had a better BPRS endpoint score (n = 38, 1 RCT, WMD -9.00, CI -17.46 to -0.54) and PANSS total score (n=38, 1 RCT, WMD - 15.90, CI -30.30 to -1.50) than chlorpromazine. Risperidone recipients noticed a significant difference for the outcome 'at least 20 % reduction' on BPRS endpoint score (n = 42, 1 RCT, RR 3.33 CI 1.07 to 10.42, NNT 3 CI 2 to 14) compared with Levomepromazine.

Table VI Levomepromazine compared to typical antipsychotics for schizophrenia [72]

Patient or population: Patients with schizophrenia **Settings:** Inpatient **Intervention:** Levomepromazine **Comparison:** Typical antipsychotics					
Outcomes	**Illustrative comparative risks* (95 % CI)**		**Relative effect (95 % CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	Typical antipsychotics	**Levomepromazine**			
Leaving the study early -	**Study population**		RR 1.11 (0.45 to 2.74)	41 (1 study)	⊕⊕ Low[1,2]
	300 per 1000	333 per 1000 (135 to 822)			

short term - any reason	**Medium risk population**				
	300 per 1000	333 per 1000 (135 to 822)			
Leaving the study early - short term - due to lack of efficacy	**Study population**		RR 0.95 (0.22 to 4.18)	41 (1 study)	⨁⨁ Low[1,2]
	150 per 1000	142 per 1000 (33 to 627)			
	Medium risk population				
	150 per 1000	142 per 1000 (33 to 627)			
Leaving the study early - short term - due to adverse events	**Study population**		RR 4.77 (0.24 to 93.67)	41 (1 study)	⨁⨁ Low[1,2]
	0 per 1000	0 per 1000 (0 to 0)			
	Medium risk population				
	0 per 1000	0 per 1000 (0 to 0)			
Leaving the study early - medium term - any reason	**Study population**		RR 2 (0.2 to 19.62)	28 (1 study)	⨁ Very Low[3,4]
	71 per 1000	142 per 1000 (14 to 1000)			
	Medium risk population				
	71 per 1000	142 per 1000 (14 to 1000)			
Leaving the study early - long term - any reason	**Study population**		RR 0.4 (0.09 to 1.81)	38 (1 study)	⨁⨁⨁ Moderate[5]
	263 per 1000	105 per 1000 (24 to 476)			
	Medium risk population				
	263 per 1000	105 per 1000 (24 to 476)			
Leaving the study early - long term - due to adverse events	**Study population**		RR 1 (0.07 to 14.85)	38 (1 study)	⨁⨁⨁ Moderate[5]
	53 per 1000	53 per 1000 (4 to 787)			
	Medium risk population				
	53 per 1000	53 per 1000 (4 to 787)			
Leaving the study early - long term- lost to follow up	**Study population**		RR 1 (0.07 to 14.85)	38 (1 study)	⨁⨁⨁ Moderate[5]
	53 per 1000	53 per 1000 (4 to 787)			
	Medium risk population				
	53 per 1000	53 per 1000 (4 to 787)			

The basis for the **assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95 % CI).*

***CI:** Confidence interval; **RR:** Risk ratio*

GRADE Working Group grades of evidence

***High quality:** Further research is very unlikely to change our confidence in the estimate of effect.*

***Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.*

***Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.*

***Very low quality:** We are very uncertain about the estimate.*

[1]*There was no information regarding allocation concealment and sequence generation. Although the study was double-blind, blinding was not tested.*

[2]*Second author had links with Janssen laboratories*

[3]*There was no information regarding allocation concealment and sequence generation. Although the study was double-blind, blinding was not tested. One patient taking chlorpromazine was omitted from the study to even up the numbers and facilitate the statistical analysis. There was also a possibility of selection bias.*
[4]*Global improvement / deterioration, mental state and behaviour assessed based on Baker-Thorpe rating scale are other outcomes not used as standard deviation not available*
[5]*The study was double-blind but the blinding was not tested.*

2.5.4.2 RELIEF OF PAIN AND ACCOMPANYING DISTRESS

2.5.4.2.1 Controlled Studies

In a double-blind crossover study of 18 patients suffering from chronic pain (cancer and arthritis), levomepromazine (15 mg) was compared with morphine (10 mg) and placebo. Three hours after intramuscular administration, levomepromazine proved to be significantly superior to placebo ($p<0.05$) and indistinguishable from morphine. Evaluations of pain relief by estimations of changes in pain intensity were found to correlate well with evaluations based on recognition of pain relief exceeding 50 % [73].

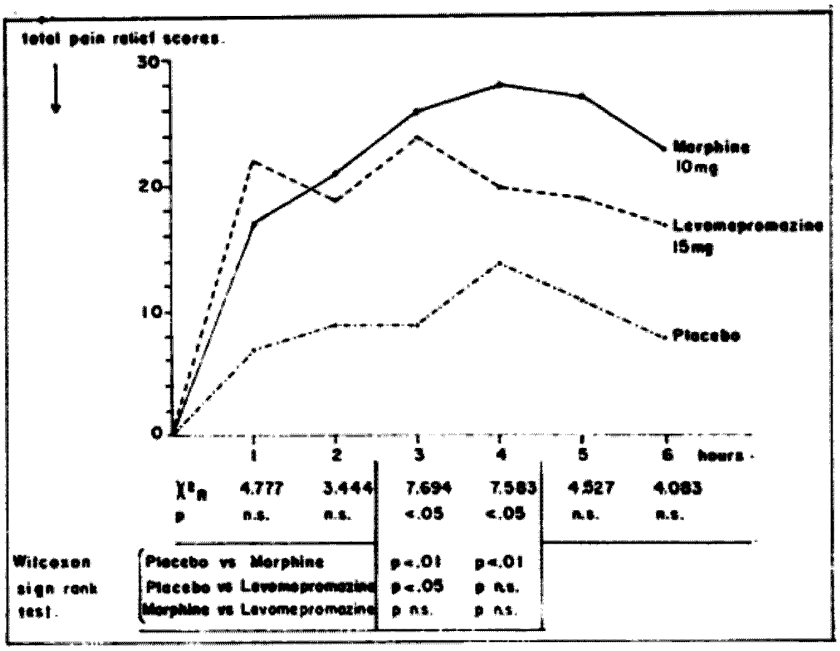

Figure 9 Total pain-relief scores for each the three medications during the six post-medication hours [73]

The relative analgesic potency of graded intramuscular doses of levomepromazine and morphine was investigated also by [redacted] in a double-blind crossover study. It was demonstrated that levomepromazine is one-half as potent as morphine and a significantly larger number of patients had side effects with levomepromazine than with morphine due to the pronounced sedative effect of levomepromazine [74].

[redacted] (1961) compared the analgesic effects of levomepromazine with those of morphine in patients suffering from postoperative or postpartum pain. The results suggested that levomepromazine when given by injection in doses of 10 to 15 mg. is a potent analgesic, and confirm the analgesic data obtained on laboratory animals. Doses of 25 mg of levomepromazine when given

by mouth for the relief of ambulatory patients with postpartum pain, however, produced side effects but did not provide analgesia which was superior to that achieved with a placebo [75].

The analgesic properties of methotrimeprazine 10 mg levomepromazine and meperidine 50 mg were compared in a blind study on 197 postoperative patients. Comparatively satisfactory pain relief was obtained with either active drug with the dosage schedule utilized [76].

Table VII Degree of relief from pain [76]

Mean score* in each drug group				
Levomepromazine	**Meperidine**	**Saline**	**F**	**p**
2.83	2.91	3.22	3.55	0.05
**Designation of Scores: 1-Excellent Relief; 2-Good Relief; 3-Fair Relief; 4-Unsatisfactory*				

Table VIII Test for a significant gap-Pain relief [76]

Drug pairs compared	**Theoretical gap (p.05) = 0.30**		
	Gap found	**Sig.**	**Drug favored**
Levomepromazine-Meperidine	0.08	NS	Levomepromazine
Levomepromazine-Saline	0.38	0.05	Levomepromazine
Meperidine-Saline	0.31	0.05	Meperidine

The efficacy of levomepromazine was evaluated in a double-blind randomized series of patients with acute myocardial infarction (AMI) [77]. Levomepromazine or pethidine were given in 328 consecutive cases to 316 patients within 24 hours after the onset of symptoms. Levomepromazine, 12.5 mg, appeared as effective as pethidine, 50 mg, in the alleviation of pain, though the initial dose had to be higher. The pain disappearance curves are presented in Figure 10.

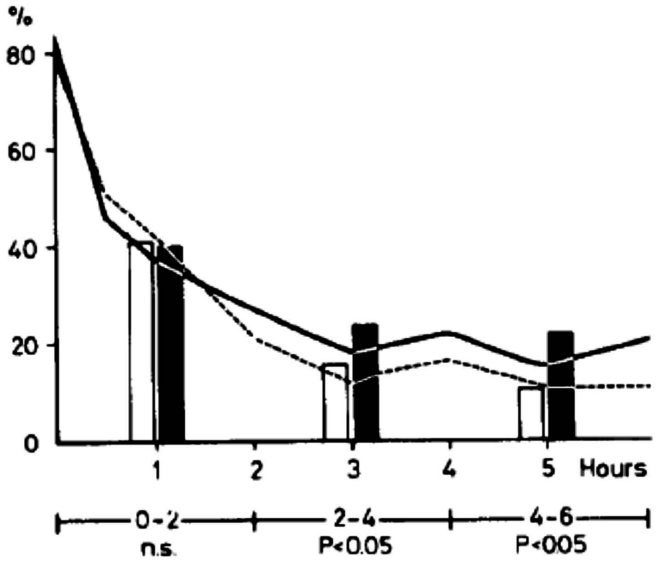

Figure 10 Pain disappearance curves and additional injections during the first 6 hours. The curves show % of patients with pain, the columns % of patients who were given additional injections. - - -, □= Levomepromazine group, ---■=Pethidine group (n.s., p>0.05) [77]

In a series of 105 patients with severe pain due to various acute and chronic conditions, 15 mg of levomepromazine hydrochloride gave pain relief comparable to that obtained with 10 mg of morphine sulphate. The method included random subcutaneous injections of two coded medications and the use of a numerical scale for recording the degrees of pain severity and sedation. The group of patients given levomepromazine had a greater average amount of pain before administration than those given morphine (3.18 versus 2.09), but nevertheless had an almost identical degree of pain relief during the first four hours after injection. The average amount of sedation was much greater with levomepromazine than with morphine [78].

On the other hand, [redacted] did not report beneficial effects of levomepromazine and clomipramine combination versus tramadol in patients with post-herpetic neuralgia, although the treatment in the comparative group was mainly with clomipramine. There were no essential differences in the current psychic/physical conditions during tramadol treatment. In the clomipramine-levomepromazine group depression and sensitivity diminished during treatment. The values of the depression and sensitivity parameters were above the values of the tramadol group from the start of the study and fell to the level of the tramadol group during therapy. The values for the dimensions activity, concentration, extroversion, self-confidence and euphoria were higher in the tramadol group than in the clomipramine-levomepromazine group [79].

The comparative study of [redacted] showed that levomepromazine is more effective than droperidol in the induction of neuroleptic anaesthesia, since levomepromazine gives a stable balanced anaesthesia, with an insignificant incidence of unpleasant psychic experiences during induction compared to droperidol. Moreover, levomepromazine appeared to reduce the need for analgesics during and after surgery [80].

2.5.4.2.2 Open Studies

The study of [redacted] revealed the analgesic and anaesthetic properties of levomepromazine. The analgesic properties were evident in the treatment of cancer pains and neuritic pains and proved to be beneficial in the treatment of rheumatic pain. The details of cases where levomepromazine was used as analgesic are presented in Table IX.

Table IX Levomepromazine as analgesic [60]

Nature of pain or disease	No. of cases	Route of administration	Average quantity	Relief alone	Potentiation of narcotics and other antalgics
Generalized cancer	39	Oral 92 % Parenteral 8 %	25 mg t.i.d.	86 %	80 %
Neuritis and neuralgia herpes zoster	16	Oral 90 % Parenteral 10 %	75 mg I.D. in 3 doses	92 %	80 %
Rheumatism and arthritis	46	Oral 100 %	15 mg I.D. in 3 doses	40 %	20 %
Postoperative analgesic	1800	Parenteral IM 100 %	75 mg I.D. in 3 doses	60-70 %	60 %
Local anaesthesia and infiltration agent	26	Parenteral	10-25 mg	100 %	Potentiates procaine

2.5.4.2.3 Reviews and Meta-Analyses

The meta-analysis of [redacted] evaluated the analgesic efficacy of antipsychotics in acute and chronic pain in adults, including studies of levomepromazine. The data from the included randomised double-blind studies showed beneficial effects of antipsychotics in the treatment of acute and chronic pain. Quantitative analysis of these studies showed a significant reduction of mean pain intensity after administration of the antipsychotic compared to placebo or another active compound, weighted mean difference (WMD) -1.78 (95 % CI -2.71 to -0.85) for the continuous data (Figure 11) [81]. Administration of Levomepromazine proved to significantly reduce the recurrence of pain within the first 72 hours after an acute myocardial infarction compared to treatment with pethidine ($p < 0.05$).

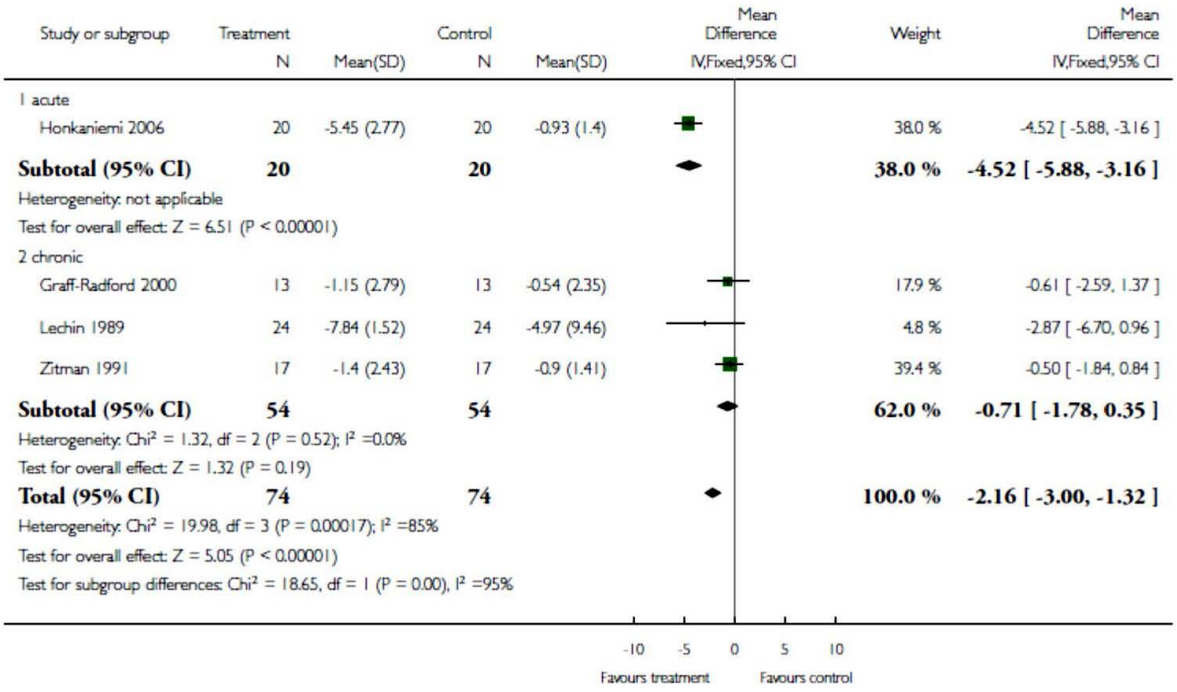

Figure 11 Reduction in pain intensity [81]

2.5.4.3 OTHER USES

2.5.4.3.1 Nausea and Vomiting

2.5.4.3.1.1 Guidelines

Current treatment of nausea and vomiting in advanced cancer mainly uses haloperidol, cyclizine or haloperidol plus cyclizine. In cases with a clear cause, the appropriate antiemetic is often effective and should be the drug of first choice. However, in many patients it is difficult to establish the cause, or the cause may be multifactorial. In these patients an antiemetic with a wider spectrum of activity may be appropriate.

Being a potent D_2, H_1, $5HT_2$ and muscarinic receptor antagonist it seems reasonable to view levomepromazine as a compound which blocks most of the receptors known to be involved in

vomiting, so its antiemetic effects are not unexpected. If selection of antiemetics by the nature of the emetic stimulus has any validity, then it would be reasonable to use levomepromazine for vomiting of multiple or unknown causes and as the second-line drug for vomiting refractory to first-line treatment. Because levomepromazine is effective as an antiemetic at much lower doses than antipsychotic or sedative doses, it does not have serious side-effects [82].

Antiemetics were then prescribed according to the aetiology-based guidelines set out in Table X.

These guidelines were based on well-known consensus-derived guidelines [83], which recommend the use of three "first-line" antiemetics, depending on the perceived cause: (a) metoclopramide, a prokinetic antiemetic; (b) haloperidol, an antiemetic acting principally in the area postrema; (c) cyclizine, an antiemetic that acts principally in the vomiting centre. The guidelines also recommend the use of levomepromazine as a "second-line" antiemetic, dexamethasone as an adjuvant agent in cases of raised intracranial pressure and hyoscine butylbromide and octreotide as adjuvant agents in cases of bowel obstruction.

Table X Aetiology-based guidelines for management of nausea and vomiting [84]

Aetiology of nausea and vomiting	"First-line" drug	"Second-line" drug
Chemical	Haloperidol (oral dose, 1.5-6 mg/24 h; parenteral dose, 3-6 mg/24 h)	Levomepromazine
Impaired gastric emptying	Metoclopramide (oral dose, 30-80 mg/24 h; parenteral dose, 30-60 mg/24 h)	Levomepromazine
Visceral/serosal	Cyclizine (oral dose, 50 mg tds; parenteral dose, 150 mg/24 h)	Levomepromazine
Cranial	Cyclizine (+dexamethasone in ↑ICP)	Levomepromazine
Vestibular	Cyclizine	Levomepromazine
Cortical	Benzodiazepines	Levomepromazine
Indeterminate causes	Levomepromazine (oral dose, 6.25-25 mg od; parenteral dose, 6.25-25 mg/24 h)	Empirical

↑ICP Raised intracranial pressure

The efficacy of the antiemetic guidelines is shown in Table XI.

Table XI Symptomatology at entry to study, at 48 h and at 1 week [84]

Symptom		No. of patients at different time points		
		No. of patients at entry to study, n=61 (n, %)	No. of patients at 48 h, n=54 (n, %)	No. of patients at 1 week, n=36 (n, %)
Nausea	None	3 (5)	24 (44)	20 (56)
	Present	58 (95)	23 (43)	12 (33)
	No data available	0 (0)	7 (13)	4 (11)
Vomiting	None	23 (38)	37 (69)	32 (89)
	Present	38 (62)	16 (29)	4 (11)
	No data available	0 (0)	1 (2)	0 (0)

A review of the existing literature related to the management of nausea and vomiting in advanced cancer showed that the drug of choice is metoclopramide titrated to effect and alternative options

include haloperidol, levomepromazine, or olanzapine. Of second-line antiemetics, only levomepromazine has evidence of benefit in prospective studies [85, 86].

The British National Formulary recommendations for the use of levomepromazine for nausea and vomiting in palliative care include the oral administration of 6 mg once daily in adults, taken at bedtime, which can be increased if necessary to 12.5–25 mg twice daily [87]. The same recommendations are available in several other guidelines [88-92].

The following studies confirm the effective use of levomepromazine for the treatment of nausea and vomiting.

2.5.4.3.1.2 *Controlled Studies*

The anti-emetic effect of levomepromazine in comparison with haloperidol was recently evaluated by [redacted] in a double-blind, randomised, controlled trial. Participants were randomised to encapsulated levomepromazine 6.25 mg or haloperidol 1.5 mg one time or two times per day and assessed every 24 hours for 72 hours. Response to treatment at 72 hours was 75 % (44/59) in the haloperidol arm and 63 % (36/57) in the levomepromazine arm with no difference between groups (intention-to-treat analysis). Complete response rates were 56 % (haloperidol) and 51 % (levomepromazine). There was no difference in response rates: (85 % (44/52) (haloperidol) and 74 % (36/49) (levomepromazine) and response rates were 64 % (haloperidol) and 59 % (levomepromazine), respectively [93].

2.5.4.3.1.3 *Open Studies*

The beneficial effects of low dose of levomepromazine in patients with advanced cancer and refractory emesis were evaluated in the open-label prospective study of [redacted] Patients were treated with subcutaneous boluses of levomepromazine (median daily dose: 6.25 mg; range: 3.12-25) and treatment was associated with a decrease in nausea from a median of 8/10 at baseline (IQR 7-8) to a median of 1 (IQR 0-2) after two days of treatment ($p < 0.0001$). Vomiting ceased in 92 % of cases. It was possible to remove the nasogastric tube from all 11 patients who had one. The study suggested that treatment with low-dose levomepromazine is an effective and safe option for advanced cancer patients who fail to respond to first-line antiemetic treatment [94].

In another open study patients with advanced malignancy were entered at different treatment levels according to symptom severity. The dose of levomepromazine was altered according to response (minimum dose 6.25 mg daily po, maximum 25 mg by 24-h subcutaneous infusion) (Table XII). Symptoms and side effects were recorded daily from 0 (baseline) to day 5 using a four-point scale. Any improvement in nausea/vomiting score was taken as a response. Sixty-five patients were entered [95].

Table XII Entry dose levels and subsequent changes. sc subcutaneous infusion, po oral [95]

Level 1 6.25 mg po/od	Level 2 6.25 mg po/bd or 6.25 mg sc/24 h	Level 3 12.5 mg po/bd or 12.5 mg sc/24 h	Level 4 25 mg sc/24 h
42 patients entered	20 patients entered[a] (18 sc, 2 po)	3 patients entered[b] (3 sc, 0 po)	0 patients entered
22 stayed on this level 15 ↑, level 2 6 ↑, level 3	5 stayed on this level 7 ↑, level 3 1 ↓, level 1	1 stayed on this level 2 ↓, level 2 2 ↑, level 4	
[a]*Five sc → po* [b]*One sc → po*			

Table XIII Control of nausea and/or vomiting (response). (CR: Complete Response, PR: Partial Response, NR: No Response, F: Fail) [95]

	CR	PR	NR	F	Overall Response
Day 2-patient assessed (n=53)	14	19	10	10	62.3 (47.9-75.2%)
Day 5-patient assessed (n=34)	12	8	9	5	58.8 (40.7-75.4%)

The cause of nausea and vomiting was multifactorial in the majority of patients, 35/65 (54 %). Of 53 patients evaluable for response at day 2, 33 (62 %) showed some improvement in nausea or vomiting. At day 5, improvement was seen in 20/34 (58 %) [95].

One hundred thirteen patients with a variety of neoplasms were enrolled in the study of Higi et al (1980). All patients had previously received cytotoxic agents known to cause vomiting (cisplatin, n=76; adriamycin, n=14; ifosfamide, n=23). The administration of levomepromazine I followed in two steps: 8-15 mg were applied orally 12 h prior treatment and the same individualized dose was again given 60 min before chemotherapy. The quality of the antiemetic effects was graded according to the following categories:

A. Complete protection
B. No vomiting but nausea still present
C. Duration and severity of vomiting reduced by 50 % or more
D. No significant effect (vomiting reduced less than 50 %)

Under clinical observation on an inpatient basis altogether 70 of 113 patients (62 %) had full protection from vomiting and nausea when two doses of levomepromazine were given 12 h and 1 h before cytotoxic chemotherapy. Another 34 % of all patients showed considerable improvement with respect to gastrointestinal side effects as experienced in previous chemotherapy courses. When the results were analysed for individual cytotoxic agents and schedules levomepromazine had its most pronounced effect in patients receiving a 5-day schedule of cisplatin. Even patients receiving 50-100 mg/m^2 of cisplatin who had previously experienced heavy gastrointestinal upsets for up to 12 h were either fully (5/13) or partially (8/13) protected. A similar antiemetic efficacy was observed in patients receiving ifosfamide or adriamycin-containing combination [96].

The same evaluation was performed in another study of [redacted] against nausea and vomiting form cisplatin chemotherapy. The quality of the antiemetic effect of levomepromazine was classified as described above.

Table XIV Effect of levomepromazine against nausea and vomiting induced by cisplatin [97]

Treatment 1 [cisplatin (20 mg/m^2 Day 1-5)] (n=63)	
Full protection (Category A)	47 (75 %)
Partial Protection (Categories B + C)	15 (23 %)
No effect (Category D)	1 (2 %)
Treatment 2 [cisplatin (100 mg/m^2 Day 1)] (n=13)	
Full protection	5 (38%)
Partial Protection	8 (62%)
No effect	0

In the case reported by [redacted] the initial dose of levomepromazine resolved the patient's nausea. Over the subsequent 20 days, the patient received a total of 23 × 6.25 mg doses of levomepromazine with good effect (at least one dose was given per day). Palliative Care Assessment Tool scores were recorded daily to assess the patient's nausea and vomiting [98]. Prior to commencement of levomepromazine, nausea and vomiting were for the most part scored at 3 (persistent and dominating her day). After the first dose of levomepromazine, nausea and vomiting scored 0. Levomepromazine remained effective throughout the patient's hospital admission [99].

2.5.4.3.1.4 *Reviews and Meta-Analyses*

A systematic review of levomepromazine from 1946 to April 2012 and peer review journals from 1980 to 2001 found seven prospective and nine retrospective studies, six case reports, and two surveys [100]. There were no randomized controlled trials, except from the study of [redacted] However, in one open label study, 60 of 70 patients (86 %) responded well to levomepromazine but there was no dose–response association [100].

Two other prospective quasi-experimental studies reported in this review also supported the effectiveness of levomepromazine [100]. [redacted] [101] also undertook a review of levomepromazine and found no related trials. An update of the latter Cochrane review identified 35 abstracts but no randomized controlled trials or additional data [102].

Table XV Recommended doses and dose ranges for levomepromazine in nausea and vomiting

Year	Study design	Mean dose (mg/day)	Dose range (mg/day)	Findings	Ref.
2010	Survey study	No data	No data	Second or third line for refractory chemotherapy-related nausea and vomiting	[86]
2006	Non-comparative prospective study	No data	6.25–25	First line in indeterminate pathophysiological causes and second line for all other causes of nausea and vomiting	[84]
2005	Open-label prospective study	6.25	3.12- 25	Second line	[94]
2004	Case report	No data	12.5 -25	First line indication: $5HT_2$ antagonist property of levomepromazine is used because large amounts of circulating 5-HT are present in carcinoid syndrome	[103]
2004	Quasi experimental prospective study	No data	6.25-25	Second line or for indeterminate pathophysiological causes	[95]
1980	Prospective study	No data	16-30	Second line in chemotherapy induced nausea	[96]
2010	SR	No data	No data	Based on [94, 95, 103]	[104]
2004	SR	No data	No data	Based on one study of Twycross, as cited in [100]	[105]

Table XVI Studies reporting effectiveness and measurement of effectiveness of levomepromazine [100]

Indication	N (patients in study)	N (patients in Levomepromazine group)	Effect	Ref.
Nausea	70	70	86 % (categorized as responders if NRS score decreased by 6+ from the baseline score)	[94]
Nausea	65	65	62.3 % (14 patients met the definition of a complete response and 19 a partial response)	[95]
Nausea	113	113	62 % (fully protected from nausea and vomiting)	[96]
Nausea	675	15	86 % (no data about how effectiveness was measured)	As cited in [100]
Nausea	29	29	83 % (no data about how effectiveness was measured)	As cited in [100]

2.5.4.3.1.5 Dosage recommendations

The extensive literature search performed by the applicant resulted in several research reports and treatment guidelines addressing the pharmacologic management of nausea and vomiting, with levomepromazine playing an important role in the palliative care concepts.

2.5 Clinical overview

In the following table (Table XVII) all available data are collected emphasizing on the widely accepted use of levomepromazine for the treatment of nausea and vomiting in palliative care.

Table XVII Guidelines and studies reporting the effective use of levomepromazine for nausea and vomiting conditions

Guideline/ Review	Condition	Dose	Effect/Comment
[106]	Nausea &vomiting associated with cancer chemotherapy	NR	Breadth of antiemetic spectrum
[107]	Anti-emetic for malignant bowel obstruction	6.25 mg (max 25 mg/day) SC	Effective. Can be sedating
[108]	Nausea & vomiting	NR	Effective.
[109]	Nausea & vomiting	Chemical/Visceral or serosal/Vestibular/Cortical/Cranial Cause: 3.125-6.25 mg oral or SC 3 times daily or 6.25-25 mg/day CSCI	Effective
[110]	Nausea & vomiting	NR	NR
[111]	Nausea & vomiting	6.25-50 mg/day	Useful as a second-line, broad-spectrum antiemetic
[112]	Nausea & vomiting	NR	NR
[113]	Refractory symptom	i.v.: 6.25-12.5 mg every 30-45 mins.c.: 12.5-25.0 mg in bolus every 45-60 min	Drug of choice
[114]	Nausea & vomiting	NR	NR
[115]	Nausea & vomiting	3 × 1-5 mg p.o.	Considered as rescue antiemetic
[85]	Nausea & vomiting	NR	Of second line antiemetics, only levomepromazine as evidence of benefit
[116]	Nausea & vomiting	PO: 6.25-25 mg 2 ×/d IM, IV: 25-50 mg/d	Palliative antiemetic choice
[117]	Nausea and vomiting	6.25mg/day	NR
[118]	Nausea and vomiting	6.25 mg – 25 mg	Reduced symptoms
[119]	Nausea and vomiting	6.25-12.5 mg SC od (or via syringe driver over 24hrs) and 6.25mg SC as required up to qds	NR
[120]	Nausea and vomiting	Oral: 6 mg-25 mg	Broad spectrum anti-emetic. Consider for refractory/persistent symptoms
[121]	Nausea and vomiting	Oral: 6.25 mg-25 mg	Broad-spectrum 'second line' antiemetic
[91]	Nausea and vomiting	6.25 to 12.5 mg nocte orally	Use 2nd line - broad spectrum
[122]	Nausea and vomiting	3 to 6 mg orally daily	Second line therapy
[93]	Cancer related nausea	6.25 mg one time or two times/day	Same response rate as haloperidol
[94]	refractory emesis	median daily dose: 6.25 mg; range: 3.12-25	Vomiting ceased in 92 % of cases

Guideline/ Review	Condition	Dose	Effect/Comment
[95]	Nausea and vomiting	Level 1: 6.25 mg po/od Level 2: 6.25 mg po/bd or 6.25 mg sc/day Level 3: 12.5 mg po/bd or 12.5 mg sc/day Level 4: 25 mg sc/day	58 % improvement
[99]	Nausea and vomiting	total of 23 × 6.25 mg doses	Dose resolved the patient's nausea
[96, 97]	Nausea and vomiting	8-15 mg oral	Full protection (75 %)
[103]	Nausea and vomiting	12.5 mg at night, increasing to 12.5 mg bd	nausea much reduced
The reviews: [84, 86, 100-102, 104, 105] summarize all above reported data.			
NR: Not Reported			

2.5.4.4 DOSAGE AND ADMINISTRATION

The dosage of levomepromazine varies with the condition under treatment and the individual response of the patient.

2.5.4.4.1 Adults

2.5.4.4.1.1 Ambulant patients

For ambulant patients, 15-30 mg levomepromazine/day is recommended (3-6 ml of levomepromazine oral solution) up to 75 - 150 mg levomepromazine/day (15-30 ml of levomepromazine oral solution).

2.5.4.4.1.2 Bed Patients with psychosis

The initial recommended total daily oral dosage is 75-100 mg (5 ml, 3 to 4 times), increased to 150 mg/day (10 ml, 3 times) up to 300 mg/day (20 ml, 3 times) and for severe psychoses up to 600 mg levomepromazine/day (40 ml, 3 times).

2.5.4.4.1.3 Bed Patients with severe pain

The initial recommended total daily oral dosage is 25-50-75 mg/day (5-10-15 ml), which is gradually increased, if necessary, up to 300 mg/day (60 ml).

If therapy with analgesics has been initiated before levomepromazine treatment, the dose of levomepromazine can be reduced. If hypnotic drugs are used concomitantly, the dose of levomepromazine should be reduced at least by half.

2.5.4.4.2 Elderly

The dose of levomepromazine in the elderly population is adjusted with special caution, since there is increased incidence of side effects.

2.5.4.4.3 Hepatic or renal impairment

The dose of levomepromazine in patients with hepatic or renal impairment is adjusted with special caution, since there is increased incidence of side effects.

2.5.4.4.4 Paediatric population

The use of levomepromazine oral solution in children and adolescents under 16 years is not recommended.

2.5.5 OVERVIEW OF SAFETY

2.5.5.1 TOXICITY

2.5.5.1.1 Adverse Events

With regards to extrapyramidal side effects, Levomepromazine had a significant advantage over typical antipsychotics (n = 79, 2RCTs, RR: 0.39 CI: 0.17-0.90, NNTB 5 CI: 2-21) (Figure 12). Levomepromazine caused less tremor (n = 41, 1 RCT RR: 0.12CI: 0.02-0.87 NNTB 3 CI: 2-8), less antiparkinsonian medication administration (n = 79, 2 RCTs, RR: 0.39 CI: 0.17-0.90, NNTB 5, CI: 2-21) compared with haloperidol. Levomepromazine caused less akathisia compared with chlorpromazine but more hypotension compared with risperidone (n = 42, 1 RCT, RR: 2.50 CI: 1.21-5.18, NNTH 3, CI: 2-7). Dizziness was common with Levomepromazine compared with other antipsychotic medications [71]

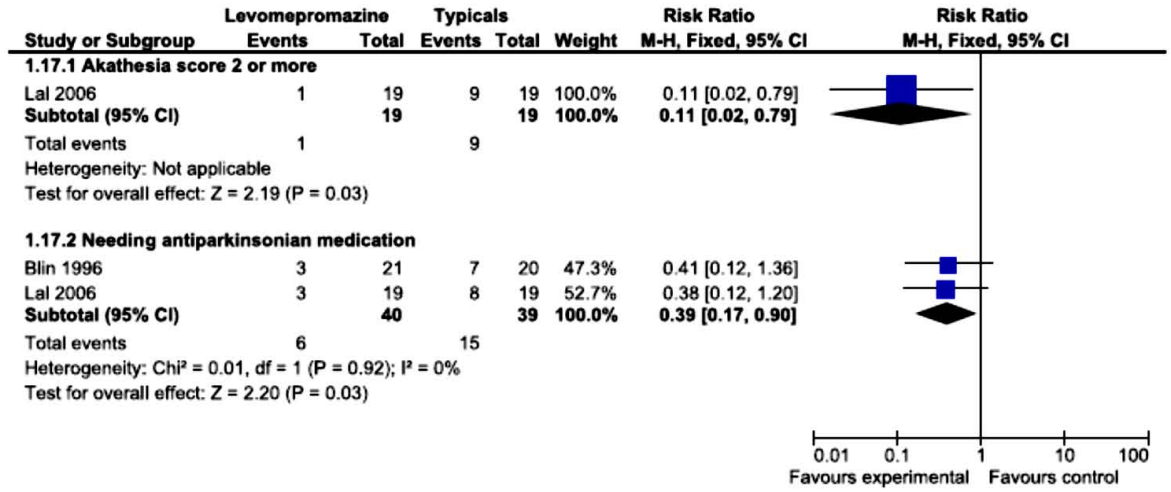

Figure 12 Adverse events: extrapyramidal side effects [71]

Levomepromazine caused less tremor (n = 41, 1 RCT RR 0.12 CI 0.02 to 0.87 NNTB 3 CI 2 to 8), less antiparkinsonian medication administration (n = 79, 2 RCTs, RR 0.39 CI 0.17 to 0.90, NNTB 5, CI 2 to 21) compared with haloperidol. Levomepromazine caused less akathisia compared with chlorpromazine, but more hypotension compared with risperidone (n = 42, 1 RCT, RR 2.50 CI 1.21 to

5.18, NNTH 3, CI 2 to 7). Dizziness was common with Levomepromazine compared with other antipsychotic medications [72].

While levomepromazine appears to have as many side effects as morphine, in its favour fewer seriously disturbing untoward effects have been reported and it is non-addicting [73].

The following adverse events have been reported after administration of levomepromazine:

2.5.5.1.1.1 *Nervous System Effects*

Extrapyramidal reactions may occur in patients receiving phenothiazines and are apparently mediated via blockade of central dopaminergic receptors involved in motor function. More than 60 % of patients receiving acute therapy with phenothiazines or other antipsychotic drugs develop clinically important extrapyramidal reactions in one form or another; some patients may develop more than one form at the same time. Acute extrapyramidal reactions produced by phenothiazines are classified into 3 major categories: dystonic reactions, feelings of motor restlessness (i.e., akathisia) and parkinsonian signs and symptoms. Chronic extrapyramidal reactions include tardive dyskinesia and tardive dystonia [24].

Neuroleptic Malignant Syndrome (NMS) may occur in patients receiving phenothiazine or other antipsychotic therapy. NMS appears to be a relatively uncommon adverse effect of phenothiazines, but the syndrome can be sudden and unpredictable in its onset, frequently is misdiagnosed, and can be fatal in 5-20 % of cases if left untreated. The syndrome usually occurs early in the course of therapy with phenothiazines or other antipsychotics, often within 1 week after treatment is initiated or dosage is increased [24].

Drowsiness, which is usually mild to moderate in severity, occurs frequently, particularly during the first weeks of therapy with some phenothiazines. Other adverse nervous system effects of phenothiazines include insomnia, restlessness, anxiety, euphoria, agitation, depression, weakness, headache, and cerebral oedema. Seizures may occur in patients receiving phenothiazines or other antipsychotic agents, particularly in patients with EEG abnormalities or a history of such disorders [24].

Adverse anticholinergic effects of phenothiazines include dry mouth (xerostomia), blurred vision, mydriasis, constipation, obstipation, nausea, atonic colon, urinary retention, decreased sweating, and impotence (difficulty achieving and maintaining an erection). Dryness of the mouth may make retention of full dentures difficult [24].

For levomepromazine, somnolence, Parkinsonism [123], convulsions [100], neuroleptic malignant syndrome [100, 124], confusional states [124] and delirium have been reported .

2.5.5.1.1.2 *Cardiovascular Effects*

Hypotension (including postural hypotension), tachycardia, increased pulse rate, syncope, and dizziness have occurred in patients receiving phenothiazines, especially with low potency phenothiazines and following the first parenteral dose of a phenothiazine, but rarely after the first oral dose. These cardiovascular effects usually subside within 30-120 minutes; occasionally they may be more severe and prolonged, resulting in a shock-like syndrome. Tolerance to the hypotensive effects of the drugs is usually developed. Marked hypotension occurs infrequently, and hypotension severe enough to cause fatal cardiac arrest has occurred rarely. Hypotension occurs most frequently when phenothiazines are given parenterally. Therefore, patients should be in a supine position at the time of parenteral administration and should remain so for at least 30-60 minutes following completion of

the injection or infusion. Patients who experience postural hypotension should be cautioned not to get up quickly and to obtain assistance when necessary. Hypotension may be a particular problem in patients with pheochromocytoma or mitral insufficiency, and severe hypotension has occurred with usual dosages in these patients. The management of antipsychotic-induced hypotension may include a variety of measures such as the use of support stockings, an increase in dietary salt intake, and/or fludrocortisone therapy. Severe hypotensive effects may be alleviated by the administration of norepinephrine or phenylephrine; epinephrine should not be used because phenothiazines cause a reversal of epinephrine's vasopressor effects and a further lowering of blood pressure. Various ECG changes, including nonspecific, usually reversible, Q- and T-wave abnormalities have occurred in some patients receiving phenothiazines [24].

For levomepromazine, QT prolongation, ventricular arrhythmias such as ventricular tachycardia or fibrillation, cardiac arrest, cardiac rhythm disturbances, sudden death/sudden cardiac death and Torsades de Pointes have been reported [125-128].

2.5.5.1.1.3 *Haematological Effects*

Leukopenia is the most frequent adverse hematologic effect associated with phenothiazine therapy. Mild leukopenia occurs in many patients who are given large doses of phenothiazines for prolonged periods; the leukocyte count generally returns to normal as treatment is continued. Agranulocytosis also has been reported and appears to occur most frequently in women, usually between the fourth and tenth weeks of therapy. Other reported adverse hematologic effects of phenothiazines include eosinophilia; thrombocytopenia; aplastic anaemia with pancytopenia, purpura, or granulocytopenia and haemolytic anaemia.

For levomepromazine agranulocytosis [129] and raised ESR [130] have been reported.

Venous thromboembolism [131], deep vein thrombosis and pulmonary embolism [131] have been also occurred.

2.5.5.1.1.4 *Dermatological Effects*

Various dermatoses, often associated with pruritus and marked photosensitivity, may occur during treatment with phenothiazines. Photosensitivity occurs infrequently in patients receiving phenothiazines and other antipsychotic drugs and is most common with the low potency phenothiazines. Patients should be instructed to avoid excessive sunlight. Other adverse dermatologic effects include urticaria, erythema, eczema, and exfoliative dermatitis. Long-term administration of high doses of phenothiazines may result in pigment depositions in various body tissues. Pigmentary changes of the skin are generally restricted to exposed areas of the body, and exposure to light appears to be a contributing factor. The pigment may also be widely distributed into the brain, heart, liver, kidneys, retina, and cornea [24].

Photosensitivity reaction and allergic dermatitis have been reported for levomepromazine [132].

2.5.5.1.1.5 *Ocular Effects*

Ocular changes including deposition of fine particulate matter in the lens and cornea have been reported in patients receiving high doses of-phenothiazines for prolonged periods of time. Pigmentary retinopathy and corneal opacities may occur during chronic therapy with the low potency phenothiazines chlorpromazine and thioridazine, particularly at high dosages. Ocular changes

reportedly occur more frequently than skin pigmentation and have occurred in patients with or without phenothiazine-induced skin pigmentation. In more advanced cases, star-shaped opacities may occur in the anterior portion of the lens. In extreme cases, visual impairment may occur. Epithelial keratopathy, lacrimation, and pigmentary retinopathy have also been reported [24].

Ocular side effects after administration of levomepromazine have not been reported.

2.5.5.1.1.6 *Gastrointestinal Effects*

Adverse gastrointestinal effects of phenothiazines include anorexia, dyspepsia, constipation, paralytic ileus, and, occasionally, diarrhoea. The "oral syndrome" consisting of dryness of the mouth; diffuse redness of mucous membranes of the mouth, loosened dentures with or without vesicles in the mouth or on the tongue, denture stomatitis, cracking of the lips and corners of the mouth, white or black, hairy tongue or bald, beefy, red tongue and thin, white pseudomembrane formation in the oral cavity has also been reported [24].

Dry mouth, constipation and Ileus paralytic necrotizing enterocolitis have been reported after treatment with levomepromazine [73].

2.5.5.1.1.7 *Endocrine and Metabolic Effects*

All first-generation (conventional) antipsychotic agents increase serum prolactin concentrations. The resultant hyperprolactinemia may lead to galactorrhoea in approximately 1 – 5 % of patients and menstrual cycle changes (e.g., oligomenorrhea) in up to 20 % of women. Mastalgia and gynecomastia also have occurred in some patients. A reduction in dosage may alleviate or decrease the severity of these adverse effects or drug therapy may be switched to an antipsychotic with less effect on prolactin (e.g., any atypical antipsychotic except risperidone). Increased appetite, hyperglycaemia, hypoglycaemia, glycosuria and high or prolonged glucose tolerance curves also have occurred in some patients [24].

Weight gain occurs with most antipsychotic agents, including in up to 40 % of patients treated with the first-generation (conventional) antipsychotic agents, with the greatest risk associated with low-potency agents. Because weight loss is difficult for many patients, prevention of weight gain is important [24].

Phenothiazines may decrease urinary gonadotropin, oestrogen and progestin concentrations and decrease vasopressin and corticotropin secretion [24].

Treatment with levomepromazine may induce glucose tolerance, impaired hyperglycaemia [133], hyponatraemia and Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) [134].

2.5.5.1.1.8 *Sensitivity Reactions and Hepatic Effects*

Sensitivity reactions and adverse hepatic effects including cholestatic jaundice, elevated hepatic enzyme concentrations, blood dyscrasias, dermatoses, and photosensitivity generally occur within the first few months after initiation of phenothiazine therapy, but occasionally they may occur following discontinuance of the drug.

Cholestatic jaundice usually occurs within 2-4 weeks after initiation of therapy in approximately 0.1-4 % of all patients receiving phenothiazines. Jaundice may also occur in neonates whose mothers have received phenothiazines during pregnancy. Phenothiazine-induced jaundice resembles infectious

hepatitis, with laboratory features of obstructive jaundice rather than parenchymal damage, and the clinician should be alert to the signs of cholestatic jaundice, including upper abdominal pain, nausea, yellow skin, influenza-like symptoms, rash, fever, and abnormal laboratory findings such as eosinophilia, bile in the urine, and elevated serum bilirubin, alkaline phosphatase, and transaminase concentrations. Laryngeal oedema, laryngospasm, bronchospasm, angioedema, and anaphylactic reactions have occurred in patients receiving phenothiazines [24]. Treatment with levomepromazine may induce jaundice, hepatocellular, cholestatic and mixed liver injury [135].

2.5.5.1.2 Precautions and Contraindications

Levomepromazine oral solution should be avoided or used with caution in the following conditions, since several adverse effects have been reported, as described in Section 2.5.5.1.1.

- Hepatic failure and end stage renal disease
- Previous cardiac disease
- Prolactin dependent tumours, such as breast tumours
- Severe hypotension or hypertension, postural hypotension
- History of brain disease or epileptic seizures
- Non-drug induced Parkinson's disease
- Atherosclerotic cerebrovascular disease
- History of Malignant Neuroleptic Syndrome
- Glaucoma
- Micturition disorder
- Pyloric stenosis
- Benign prostatic hyperplasia
- Congenital long QT syndrome or other clinically significant cardiac disorders (especially coronary artery disease, conduction disorders, arrhythmias)
- Concomitant treatment with drugs that prolong the QT interval in the ECG or cause hypokalaemia

Blood count should be checked regularly before treatment with neuroleptics and if blood values are outside the normal range, levomepromazine should not be used [136, 137].

The cardiovascular effects of levomepromazine have been described previously (Section 2.5.5.1.1.2). Since levomepromazine prolongs the QT interval, the proposed product should be avoided in patients with cardiac disorders. Furthermore, the CNS effects of levomepromazine are also described in Section 2.5.5.1.1.1 and the proposed product should be administered to patients with history of NMS, other brain diseases or epileptic seizures.

An approximately 3-fold increased risk of cerebrovascular adverse events with some atypical antipsychotics has been reported in dementia population. Therefore, levomepromazine oral solution must be used with caution in patients with risk factors for stroke [138].

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with levomepromazine solution and preventive measures should be undertaken [131].

Levomepromazine oral solution should not be used in:

- acute alcohol-, sleeping medication-, analgesic- and psychopharmaceutical- intoxication
- shock (circulatory failure)
- coma
- impairment of the hematopoietic system

2.5.5.1.3 Special Populations

2.5.5.1.3.1 *Use in the Elderly*

Literature data indicated that elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of mortality. The extent to which this association is attributable to the medicinal product, as opposed to being confounded by patient characteristics, has not yet been elucidated [138].

Levomepromazine oral solution is not indicated for the treatment of dementia-related behavioural disturbances.

2.5.5.1.3.2 *Use in Children*

The use of levomepromazine oral solution in children and adolescents under 16 years is not recommended.

2.5.5.1.3.3 *Use in hepatic and renal impairment*

Levomepromazine is contraindicated to patient with hepatic failure or end stage renal disease.

Initiation of treatment with levomepromazine should be followed by monitoring of liver function every 6-12 months.

2.5.5.1.3.4 *Fertility, Pregnancy and Lactation*

Neonates exposed to antipsychotic agents, including phenothiazines, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Symptoms reported included agitation, hypertonia, hypotonia, tardive dyskinetic- like symptoms, tremor, somnolence, respiratory distress, and feeding disorder [24].

Safety of phenothiazines during pregnancy has not been established. Animal reproduction studies have not been performed with most of the phenothiazines.

It is not known whether phenothiazines can cause foetal harm when administered to pregnant women. Although several retrospective studies of infants born to women treated with a phenothiazine (e.g., chlorpromazine, trifluoperazine) have found no increased risk of adverse foetal effects associated with phenothiazine use, one study found an increased risk of malformations [24].

In addition, prolonged jaundice, extrapyramidal symptoms, hyperreflexia, and hyporeflexia have occurred in some neonates born to women who were receiving phenothiazines during pregnancy. Phenothiazines should generally be used during pregnancy only when the potential benefits justify the possible risks to the foetus [24].

The effect of phenothiazines on fertility in humans is not known. Impotence, increased or decreased libido, inhibition of ejaculation, amenorrhea, and menstrual irregularities have occurred in some individuals during phenothiazine therapy [24].

Phenothiazines are distributed into milk [24].

2.5.5.1.3.5 *Other special populations*

Other special precautions that should be considered during levomepromazine treatment were not identified in the public literature.

2.5.5.1.4 Effects on Ability to Drive and Use Machines

As described in previous sections, levomepromazine may cause tiredness, dizziness and fatigue which may affect the patient's ability to drive or operate machinery. Patients should avoid the performance of potentially dangerous tasks, which require alertness and good concentration, such as driving a motor vehicle or operating machinery, at any time when affected.

Simultaneous intake of alcohol may further affect the ability to drive and use machines [139].

2.5.5.1.5 Overdose and Treatment

The symptoms of levomepromazine overdose are somnolence to coma, confusion and agitation, cardiac failure, arrhythmia, hypotension, tachyarrhythmia, dry mucous membranes, constipation, paralytic ileus, urinary retention, mydriasis, convulsions, hypo- or hyperthermia, parkinsonism [140].

Initial treatment consists of induction of emesis. Gastric lavage can be attempted many hours after ingestion of a toxic dose by using high amounts of lubricant due to the existing dry mucous membranes. Activated charcoal and Glauber's salt can be administered repeatedly to inhibit the absorption and accelerate the elimination of levomepromazine. The antidote is physostigmine due to its anticholinergic properties. The risk with physostigmine treatment should be weighed against its benefit on the management of levomepromazine overdose [141].

Symptomatic treatment such as controlled ventilation and intubation may be considered, as well as general intensive medical care for restoring electrolyte balance, serum tonicity, through intravenous infusion of positive inotropic agents, ECG and intraocular pressure monitoring. Furthermore, infusion of alpha sympathomimetics such as norfenefrine or noradrenaline may be considered [142]. The use of adrenaline is not recommended. Severe dystonic reactions usually respond to biperiden (adults: 2.5-5 mg IM or slow IV) or diphenhydramine (50 mg orally every 6 hours) or diazepam (3-10 mg slow IV) [143].

2.5.6 BENEFITS AND RISKS CONCLUSIONS

2.5.6.1 THERAPEUTIC CONTEXT

2.5.6.1.1 Disease or Condition

Schizophrenia is the most common functional psychotic disorder, and individuals with the disorder can present with a variety of manifestations. On the other hand, manic-depressive illness, in which manic

episodes are occurred, is another common, severe, long-term condition. Both conditions affect a large number of the population and in both cases the presence of psychomotor restlessness and agitation is very common. Agitation can appear suddenly or slowly and last a few minutes or for an extended period of time. The aim of the treatment of such conditions is to alleviate the symptoms and allow a return to usual levels of psychosocial functioning. Levomepromazine can achieve a rapid control of agitation and ensures the safety of patients.

In the cases of terminal illness, several common symptoms must be also managed and levomepromazine is an effective agent for the relief of severe pain, with also good performance as an anti-emetic agent.

2.5.6.1.2 Current Therapies

Agitation requires prompt and safe intervention. There are several approaches for the management of agitated patients. In patients for whom non-pharmacological treatments fail or are not indicated three classes of medications are employed: first generation antipsychotics, benzodiazepines and second-generation antipsychotics.

Levomepromazine, as neuroleptic, has been evaluated in several clinical studies for its efficacy and safety in psychomotor restlessness and agitation in the presence of psychotic disorders.

Additionally, in terminal illness and in order to manage the symptom of pain, combinations of therapies are used. Levomepromazine is used in combination with other medications and several studies have revealed the beneficial effects of such combinations.

The planned medicinal product will be available as oral solution at the strength of 25 mg/5 ml in terms of levomepromazine, as levomepromazine hydrochloride.

2.5.6.2 BENEFITS

Levomepromazine is an aliphatic phenothiazine type of neuroleptic, chemically related to chlorpromazine and trifluorpromazine.

The clinical efficacy of levomepromazine for the suppression of psychomotor restlessness and agitation within the context of psychotic disorders and agitation states in manic episodes has been evaluated in clinical studies and has been compared to other medications. The results of clinical studies indicate that levomepromazine is effective in these episodes when compared to other medications such as haloperidol and olanzapine. The results of clinical studies support also the used of levomepromazine in combination with other medications such as morphine for the treatment of serious or chronic pain in terminal illness. There is also evidence that levomepromazine is effective in palliative care and especially in nausea and vomiting and it is already used in clinical practice, although this clinical experience is not supported by numerous clinical trials.

2.5.6.3 RISKS

Symptoms of overdose included mostly cardiovascular disorders, such as heart rhythm disorders, hypotension and tachycardia. However, in most of clinical studies included in this review, no serious adverse events were reported and, in most cases, levomepromazine had fewer adverse reactions compared to other medications. In special populations (elderly or children), the dose should be adjusted and monitored.

The most common adverse events occurring after levomepromazine administration are gastrointestinal disorders and nervous system disorders. The effect of levomepromazine, along with other antipsychotic medications, on QTc prolongation is well known and monitoring after levomepromazine administration is recommended.

2.5.6.4 BENEFIT-RISK ASSESSMENT

Levomepromazine has a well-established pharmacological and clinical profile and is in use for many years. The efficacy of levomepromazine as a neuroleptic agent has been studied since 1960. Levomepromazine is a useful medication for the management of psychomotor restlessness and agitation in psychotic disorders. Additionally, levomepromazine is a useful medication when combined with other drugs for the treatment of chronic and/or severe pain in terminal illness.

Based on the extensive analysis of literature data, it can be stated that the therapeutic benefit clearly outweighs the possible risk associated with the use of levomepromazine as recommended by the applicant.

2.5.6.5 APPENDIX

2.5.6.5.1 Effect of excipients

A comparison between the qualitative composition of the reference product and the product under assessment is presented in Table XVIII.

Table XVIII Qualitative composition of reference product and proposed formulation

Reference product (Neurocil Tropfen 40 mg/ml)	Proposed formulation (Levomepromazine 25 mg/5 ml Oral Solution)
Ascorbic acid	-
Anhydrous citric acid	-
Ethanol	-
Glycerol	**Glycerol**
Sucrose	**Saccharin Sodium**
Orange essence	**Orange flavour**
Vanilla essence	-
Sugar caramel	-
Purified water	Purified water
-	Propylene Glycol
-	Sodium Benzoate
-	Hydrochloride Acid

The quantitative composition is presented in Table XVIII.

The reference product contains 21.5 % vol. ethanol. According to the SmPC of Neurocil Tropfen 40 mg/ml, 1 drop (from dropper bottle) corresponds to 1 mg of levomepromazine. The volume administered for 25 mg dose is 0.625 ml, since 25 drops correspond to 25 mg and 40 drops are equal to 1 ml. The amount of sucrose of the reference product is 200 mg per ml, as stated in its Patient Leaflet. [redacted]

Table XIX Quantitative comparison of reference product and proposed formulation as regards the excipients

Neurocil Tropfen 40 mg/ml			Levomepromazine 25 mg/5 ml Oral Solution		
Excipient	**Quantity per ml**	**Quantity per 25 mg dose**	**Excipient**	**Quantity per ml**	**Quantity per 25 mg dose**
Ethanol	[redacted]		Propylene Glycol	[redacted]	
Glycerol			Glycerol		
Anhydrous citric acid			Sodium Benzoate		
Sucrose			Saccharin Sodium		
Ascorbic acid			Orange Flavour		
Orange essence			Hydrochloric acid		
Vanilla essence					
Sugar caramel					
Purified water					

[redacted]

2.5 Clinical overview