2.4 Non Clinical Overview

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2.4.1 OVERVIEW OF THE NONCLINICAL TESTING STRATEGY

2.4.1.1 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)	

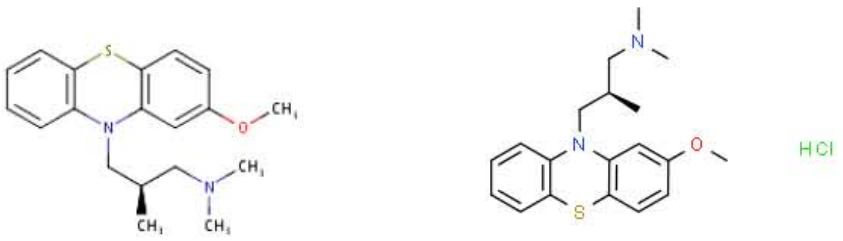


Figure 1: Chemical structure of Levomepromazine (on the left) and levomepromazine hydrochloride (on the right) [1]

2.4.1.2 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 proposed indications, dosage and adverse events of the product under assessment are the same as the reference product, and more specifically it is indicated for:

- 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.

2.4.1.3 NON CLINICAL DEVELOPMENT PROGRAM

The current nonclinical evaluation is based on the applicable European Guidelines for the evaluation of hybrid 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 Nonclinical Overview are provided in Module 4.

2.4.1.4 SEARCH STRATEGY

This Nonclinical Overview examines the current state of published scientific knowledge available on the nonclinical 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 Nonclinical 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 Nonclinical overview the search terms included the keywords "levomepromazine" or "methotrimeprazine" coupled with "pharmacology", "pharmacodynamics", "pharmacokinetics", "toxicity" or "toxicology" and the results were limited to "other animals". 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 June 2020 the search term "levomepromazine" limited "other animals" yielded about 218 results in the PubMed database. Since levomepromazine has a well-established medicinal use, a number of representative articles was selected to compile this report.

2.4.2 PHARMACOLOGY

2.4.2.1 PRIMARY PHARMACODYNAMICS

2.4.2.1.1 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 [2, 3].

Levomepromazine has a broad receptor binding profile 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 [4] resulting in the following effects:

- Anti-dopaminergic Effect
- Anti-histaminic Effect
- Anti-serotonergic Effect
- Alpha-Adrenergic Receptor-Blocking Effect
- Anticholinergic Effect

In vitro and in vivo studies evaluating the binding affinity of levomepromazine in these sites and its relevant actions are presented in the following sections.

2.4.2.1.2 In vitro studies

The binding affinity of levomepromazine to several receptors has been investigated by [redacted] and the results are presented in Table II.

2.4 Nonclinical overview

Table II Receptor binding profile in human brain[a] [4]

Receptor (Ligand)	K_D (nM, x ± SE) [Relative affinity (%)[b]]		
	Levomepromazine	Clozapine	Chlorpromazine
Muscarinic-M_1 (^{3}H-pirenzepine)	127 ± 19 [19 %] (n=6)	23.9 ± 3 [100 %] (n=5)	134 ± 21 [18 %] (n=6)
Muscarinic-M_2 (^{3}H-AF-DX38)	285 ± 76 [42 %] (n=5)	120 ± 22 [100 %] (n=5)	570 ± 120 [21 %] (n=5)
Adrenergic α_1 (^{3}H-prazosin)	0.57 ± 0.16 [3421 %] (n=6)	19.5 ± 1.8 [100 %] (n=5)	4.4 ± 1.1 [443 %] (n=6)
Adrenergic α_2 (^{3}H-rauwolscine)	583 ± 104 [27 %] (n=4)	159 ± 16 [100 %] (n=4)	980 ± 65 [16 %] (n=3)
Serotonin 5HT-1 (^{3}H-serotonin)	594 ± 144 [57 %] (n=3)	338 ± 54 [100 %] (n=3)	752 ± 42 [45 %] (n=3)
Serotonin 5HT-2 (^{3}H-ketanserin)	18.5 ± 1.6 [176 %] (n=3)	32.6 ± 3.7 [100 %] (n=3)	41.3 ± 1.2 [79 %] (n=3)
Dopamine D_1 (^{3}H-SCH 23390)	493 ± 268 [153 %] (n=3)	753 ± 326 [100 %] (n=3)	444 ± 32 [170 %] (n=3)
Dopamine D_2 (^{3}H-spiperon)	21 ± 5.9 [2900 %] (n=3)	609 ± 122 [100 %] (n=3)	32.3 ± 3.4 [1885 %] (n=3)

[a]Frontal cortex except for D_1 and D_2 which were studied in striatum (caudate nucleus and putamen combined)
[b]Relative affinities (%) are given after setting clozapine values at 100 %

The most recent study of [redacted] confirmed the anti-cholinergic effects of levomepromazine along with other antipsychotics by investigating the inhibitory effects on [N-Methyl-^{3}H]Scopolamine specific binding in mouse cerebral cortex. At 10^{-5} M levomepromazine inhibited [N-Methyl-3H]Scopolamine binding by > 45 % [5].

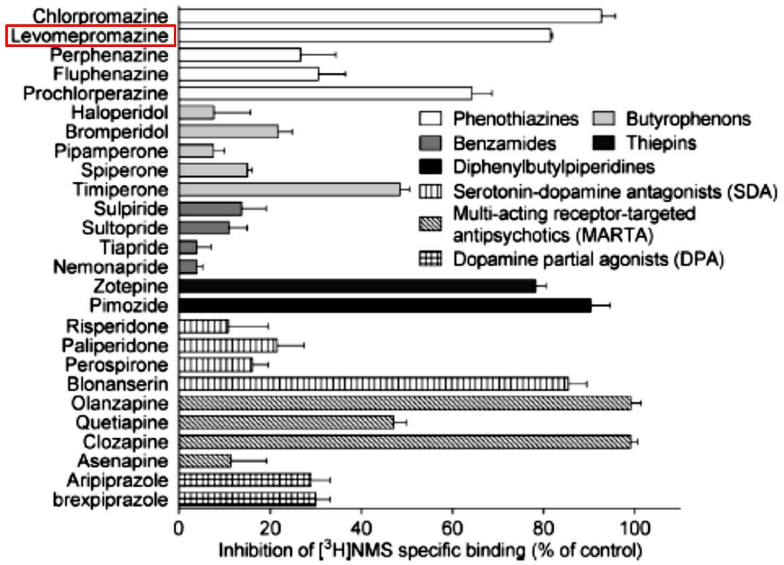


Figure 2 Inhibitory effects of phenothiazines, butyrophenons, benzamides, thiepins, diphenylbutylpiperidines, serotonin-dopamine antagonists (SDA), marti-acting receptor-targeted antipsychotics (MARTA) and dopamine partial agonists (DPA) (each at 10^{-5} M) on specific binding of 0.5 nM [^{3}H]NMS in mouse cerebral cortex [5]

It has been also demonstrated that levomepromazine induces autophagy in neuronal or other cell types, mainly through AMPK-mediated mTORC1-independent mechanisms. This induction of autophagic response might contribute to reducing neuronal dysfunction in schizophrenia, but also to the adverse effects associated with its long-term use, including brain volume loss and weight gain [6, 7].

2.4.2.1.3 In vivo studies

The effects of levomepromazine on intracranial self-stimulation behaviour have been investigated in rats with chronic electrodes implanted in the lateral posterior hypothalamus. Levomepromazine showed dose-related effects in depressing self-stimulation. The ED_{50} values of levomepromazine are presented in Table III indicating that levomepromazine has a selective depression of self-stimulation.

Table III Levomepromazine effects on self-stimulation and rotarod performance in rats [8]

ED_{50} (95 % Confidence Limits)	**Self-stimulation (a)**	2.48 (1.36 – 4.53)
	Rotarod (b)	6.12 (4.31 – 8.69)
	Ratio (b/a)	2.47

The central actions of levomepromazine were investigated in rabbits by [redacted]. Experiments were performed on unanesthetized albino rabbits of both sexes and the various brain structures were recorded. A single dose of levomepromazine (1 mg/kg) caused a marked slow wave pattern in the cortical EEG and an irregular and slow wave pattern in the hippocampal EEG. In the same dose of 1 mg/kg, levomepromazine markedly suppressed EEG arousal response evoked by the tooth pulp stimulation (325 % increase in the threshold voltage) and moderately depressed that induced by the sciatic stimulation (88 % increase in the threshold voltage) or acoustic stimulation [9].

By assessing EEG spectral changes in the prefrontal and sensorimotor cortex in conscious rats [10], the study of [redacted] evaluated the effects of a range of antipsychotics compounds with the aim to compare the different classes of compounds and to assess if the receptor profiles correlate with EEG spectra. A peak effect was observed at one frequency for most of the drugs: it was at 10 Hz for quetiapine (2.5 mg kg^{-1}) and chlorpromazine (0.5 mg kg^{-1}). The amplitude of synchronization at 15-20 Hz was dependent on the drug. It was particularly low for clozapine (5 mg kg^{-1}), levomepromazine (1 mg kg^{-1}) and risperidone (1 mg kg^{-1}) [11].

On the other hand, the antiemetic effects of levomepromazine along with other anti-emetic agents have been studied in dogs, in which vomiting has been induced by apomorphine or copper sulphate. Where vomiting was due to stimulation of the emetic trigger zone (as with the administration of apomorphine), phenothiazines, related agents and trimethoxy-benzamide were dearly superior anti-emetics to those agents belonging to other chemical groups [12]. All phenothiazines tested were highly effective with the exception of promazine.

The effects of single and chronic administration of Levomepromazine on the behaviour of rats in the forced swimming test have been evaluated. Reduction in immobility in this test is regarded as an indicator of a possible antidepressant action and has been shown at dose levels which otherwise decrease activity in the open field test.

Table IV Effects of Acute and Chronic treatment with Levomepromazine on the immobility in the forced swimming test in rats [13]

Dose (mg/kg)	Acute Immobility (sec) Mean ± SEM	% Control	Chronic Immobility (sec) Mean ± SEM	% Control
0	260.5 ± 9.3	100	252.2 ± 5.9	100
0.5	259.2 ± 9.7	99.5	246.4 ± 8.4	97.7
1.5	221.9 ± 8.3*	85.2		
5.0	231.7 ± 14.2	88.9		
15.0	254.7 ± 5.2	97.8		

Table V Effects of Chronic treatment with Levomepromazine on behavioural parameters in the open field in rats [13]

Treatment		Ambulation		Rearings	Grooming	Defacation
		1	2	3	4	5
Solvent	Mean	75	39	16	3	3
	SEM	13	8	2	1	1
	%	100	100	100	100	100
Levomepromazine	Mean	82	41	20	4	5
	SEM	8	7	1	1	1
	%	109	105	130	126	140

Levomepromazine was administered in a dose of 1.5 mg/kg orally, twice daily for 10 days. The test was performed 15- 18 hr after the last dose.
1. *Time of ambulation in seconds/3 min.*
2. *Number of sectors crossed/3 min.*
3. *Number of times animal removed forepaws from the floor/3 min.*
4. *Times animal groomed/3 min.*
5. *Numbers of faecal boli excreted/3 min. Mean values ± SEM of 9-10 rats*

These results indicate that Levomepromazine shortened the immobility period in the force swimming test after single oral administration [13].

2.4.2.2 SECONDARY PHARMACODYNAMICS

2.4.2.2.1 In vitro studies

Phenothiazine derivatives are known to be able to produce electrocardiographic abnormalities in patients receiving therapeutic doses. The study of [redacted] comprised a comparison of the action of monodesmethyl-levomepromazine with the action of levomepromazine and levomepromazine sulfoxide on isolated rat atria and studied also the ability of those agents to reduce acetylcholine-induced changes in ERP. The following figures indicate that monodesmethyl-levomepromazine must be considered pharmacologically active. Both monodesmethyl-levomepromazine and levomepromazine decreased the contractile force and the excitability of the isolated rat atria in a dose-dependent manner and to a very similar extent [14].

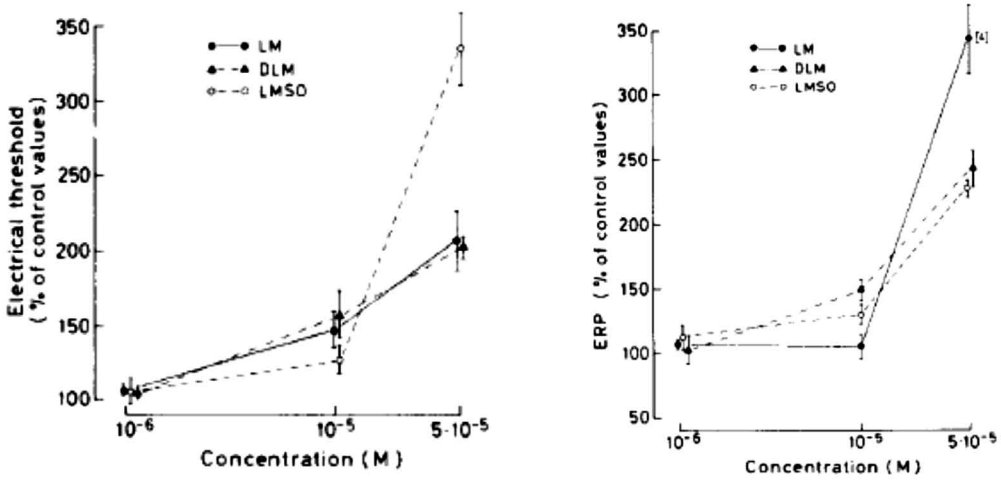


Figure 3 Effects on threshold for electrical stimulation 30 min after addition of levomepromazine (LM), monodesmethyl-levomepromazine (DLM) or levomepromazine sulfoxide (LMSO) (on the left) and effects on effective refractory period (ERP) measured 30 min after addition of levomepromazine (LM), monodesmethyl-levomepromazine (DLM) or levomepromazine sulfoxide (LMSO) (on the right) [14]

Levomepromazine has been shown to exhibit antibacterial properties in vitro. The susceptibility of twelve slow growing mycobacteria to levomepromazine was investigated and reported by [redacted] (Table VI).

Table VI The Susceptibility of 12 slow-growing Mycobacteria to levomepromazine maleate [15]

Strain	Levomepromazine maleate (µg/ml)
M. Tuberculosis St 5	25
M. Kansasii R 2275	50
M. Kansasii R 7228	25
M. Scrofulaceum T 14447	50
M. Intracellulare T 7360	50
M. Intracellulare R 8656	25
M. Intracellulare V 915	50
M. Intracellulare R 6550	50
M. Intracellulare R 7313	25
M. Intracellulare R 8411	25
M. Intracellulare R 8588	50
M. Intracellulare R 1631	50

The in vitro activity of levomepromazine against M. tuberculosis has been also reported by [redacted] [16].

2.4.2.2.2 In vivo studies

The sedative and antinociceptive effects of levomepromazine, were studied in rats and mice using three behaviour evaluation methods. Both exploratory behaviour and spontaneous locomotor activity were significantly diminished in a spontaneous locomotor activity test in open field when using levomepromazine [17]. Figure 4 shows the results related to the antinociceptive effects of levomepromazine, azaperone and midazolam in the writhing reflex in mice. In this test, all drugs

examined were able to abolish the writhing reflex, establishing an appropriate antinociceptive effect with respect to visceral pain in mice, evoked by the injection of 0.6 % acetic acid.

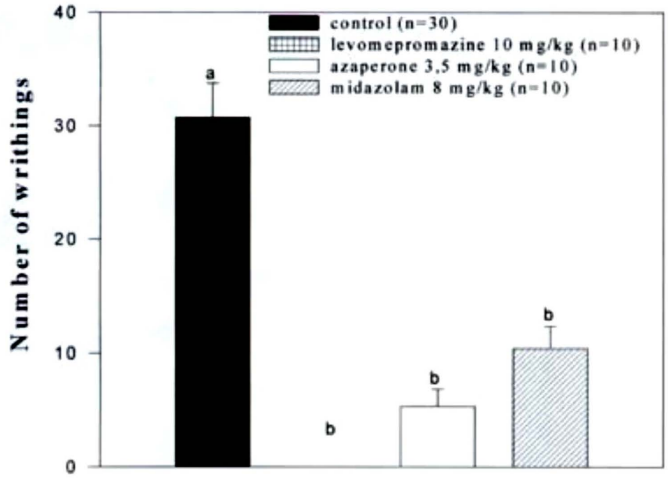


Figure 4 Antinociceptive effect of levomepromazine (10.0 mg/kg), azaperone (3.50 mg/kg) and midazolam (8.0 mg/kg), evaluated by the writhing test in mice [17]

The sedative and antinociceptive effects of levomepromazine were also investigated by [redacted] in horses. Sedation was evaluated by determining the Spontaneous Locomotor Activity (SLA) in automated individual behaviour stalls and by measuring Head Ptosis (HP). The intravenous injection of acepromazine (0.05; 0.08 and 0.11 mg/kg) and azaperone (0.25; 0.5 and 1.0 mg/kg) did not induce significant changes on SLA. In contrast, intramuscular injection of levomepromazine caused an increase in SLA at the dosages of 0.75 and 1.0 mg/kg, but not at 0.5 mg/kg. Significant head ptosis occurred with all dosages and drugs. Antinociception was determined utilizing a heat projection lamp to record the Hoof Withdrawal Reflex Latency (HWRL) and Skin Twitch Reflex Latency (STRL). Acepromazine (0.08mg/kg) and levomepromazine (0.75mg/kg) did not induce significant changes on both HWRL and STRL, but azaperone (0.5 mg/kg) produced a significant increase in both HWRL and STRL [18].

2.4.2.3 SAFETY PHARMACOLOGY

The CNS and cardiovascular effects of levomepromazine are well known and presented in the following subsections. Extrapyramidal reactions, neuroleptic malignant syndrome and seizures have been reported to patients receiving levomepromazine. Levomepromazine does prolong the QT interval.

However, these effects have been reported rarely and are not expected the affect the safety profile of levomepromazine.

2.4.2.3.1 Central Nervous System

Central nervous system side effects have been reported for phenothiazines. Extrapyramidal reactions may occur which can be divided into acute and chronic reactions. Acute extrapyramidal reactions are signs and symptoms that develop during the first days and weeks of phenothiazine or other antipsychotic agent administration, are dose related, and are reversible upon dosage reduction or discontinuance of the drug. 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. Neuroleptic malignant syndrome (NMS) may occur in patients receiving phenothiazines [19]. NMS has been characterized by hyperthermia, severe extrapyramidal dysfunction (including severe hypertonicity of skeletal muscles), varying levels of consciousness (including stupor and coma), altered mental status (including catatonic reactions), and autonomic instability (including cardiovascular effects such as hypertension and tachycardia) [19].

Levomepromazine has been reported to have an augmentative action on SWS, and in small dosage they possibly have a slight augmentative action on REM sleep. The effects of levomepromazine 5 mg on two models of sleep-wake schedule change-6 hours advanced shift: (A-shift), and 6 hours delayed: (D-shift) - were investigated in 6 healthy volunteers using polysomnography. In the A shift, levomepromazine did not decrease XSWS, however it increased the % SR and accordingly improved REM/NREM. However, levomepromazine showed no sleep-inducing effect [20].

[redacted] reported paroxysmal EEG activity in patients undergoing treatment with levomepromazine. The EEG-records and seizures after levomepromazine treatment are presented in Table VII.

Table VII EEG-Records and Seizures after levomepromazine treatment [21]

Mean dosage (mg)	500
Patients	72
Records	88
Abnormal EEG %	31
Generalised transient disturbances (Paroxysmal)	1
Generalised transient disturbances (Non-Paroxysmal)	18
Seizures	-

2.4.2.3.2 Cardiovascular System

Some studies have revealed a relatively high prevalence of QT prolongation in patients treated with a range of (sometimes unspecified) antipsychotics [22, 23] and in one study QTc dispersion was also increased [23]. Sudden death has occasionally been linked to the use of thioxanthines [24] and other phenothiazine antipsychotics such as perphenazine and levomepromazine [25].

According to the latest review of [redacted] levomepromazine has been categorized as class B drug (i.e. propensity of QTc prolongation) [26].

The low-potency antipsychotic drugs chlorpromazine and levomepromazine have only been reported to prolong the QTc interval when given in high doses (100 mg) [27, 28].

Table VIII Cardiovascular risk stratification of commonly used antipsychotics [26]

Antipsychotics	Cardiovascular Adverse Effects								
	ST	OH	HT	QTcP	TdP[a]	BrS	MI	M	C
Amisulpride				++	+++		+++		+
Aripiprazole	+	++		+	+				
Asenapine		+		+	+				
Chlorpromazine	++	++		++	+++			+	
Chlorprothixene				++	++				
Clothiapine						+			
Clozapine	+++	+++	+++	++	+++		+	+++	+++
Cyamemazine				+++	+++	+			
Flupentixol				++	+				
Fluphenazine		+		++	++			+	
Haloperidol[b]		+		+++	+++	+		+	
Iloperidone		++		+	+				
Levomepromazine				++	++				
Loxapine				+	+	+			
Lurasidone		+		+	+				
Olanzapine	+	++	++	+	+++			+	
Paliperidone				++	+				
Perphenazine		+	+++	+	+				
Pimozide				+++	+				
Quetiapine	++	+++	+	++	+++			+	+
Risperidone	++	++	+	++	+++		+	+	
Sertindole				+++	+++				
Sulpiride				++	+				
Trifluoperazine				+	+	+			
Ziprasidone	+	++	++	+++	+++				
Zuclopenthixole				+	+				

Low Risk (+), Moderate Risk (++), and High Risk (+++).
[a]Additional TdP data from [29]
[b]Extremely increased risk with a total cumulative dose of IV haloperidol > 2 mg.
BrS: Brugada syndrome, C: Cardiomyopathy, ECG: Electrocardiogram, HT: Hypertension, IV: Intravenous, MM: Myocarditis, MI: Myocardial infarction, OH: Orthostatic hypotension, QTcP: Corrected MQT prolongation, SCD: Sudden cardiac death, ST: Sinus tachycardia, TdP: Torsades de Pointes.

The cardiovascular effects of levomepromazine have been investigated following intracoronary injection in dogs by [redacted] A variety of changes influencing the configuration of the T wave in the form of inversion, terminal lipping and rounding of the peak were induced by levomepromazine. These E.C.G. changes give an indication of direct effect of these drugs on ventricular myocardium [30].

The effects of levomepromazine and its sulfoxide has been studied on spontaneously beating and on electrically driven rat atria in vitro. Levomepromazine and levomepromazine sulfoxide produced a dose-dependent decrease in the work index of spontaneously beating atria and in the contractile force of electrically driven atria. At higher concentrations, levomepromazine sulfoxide caused a pronounced increase in the threshold for electrical stimulation and the effective refractory period [31].

[redacted] confirmed that levomepromazine induce myocardial lesions to rabbits after treatment of rabbits with 3 mg/kg/day for three months, however these effects have not been demonstrated on long-duration or in pre-existing cardiac lesions [32].

The induced QT prolongation and Torsades de Pointes by Levomepromazine have been reported also to other studies [28, 33, 34].

Table VIII summarizes the cardiovascular adverse effects of several antipsychotics and shows that levomepromazine has a medium to low risk for cardiovascular abnormalities.

2.4.2.3.3 Respiratory System

Levomepromazine in combination with etorphine has been reported to produce severe respiratory depression with consequent hypercapnia and acidosis in rabbits [35].

Studies reporting other effects on levomepromazine alone or in combination with other neuroleptics on respiratory system were not available in the public domain.

2.4.2.4 PHARMACODYNAMIC DRUG INTERACTIONS

2.4.2.4.1 Effects of other medicinal products on levomepromazine

The effects of levomepromazine can be inhibited by anticholinergic medicinal products, such as biperiden [36].

The moderate anticholinergic effects of levomepromazine can be enhanced by other anticholinergic agents or other medicinal products with anticholinergic effects [37].

2.4.2.4.2 Effects of levomepromazine on other medicinal products

The concomitant use of levomepromazine with analgesics, hypnotic agents, sedatives or other CNS antidepressants can lead to increased sedation and respiratory depression [37].

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 [38].

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 [37].

The combined use of levomepromazine with dopamine agonists (e.g. levodopa) may result in diminished effects of dopamine agonists [39]. 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 [40].

2.4.2.4.3 Other drug interactions

The concomitant use of levomepromazine and piperazine anthelmintics and metoclopramide can result to an increased risk of extrapyramidal symptoms [41].

Treatment with levomepromazine may affect the PKU Test for Phenylketonuria (false-positive result) [42].

The concomitant used of medicinal products that prolong the QT interval (class IA or III antiarrhythmics, cisapride, certain antibiotics, antimalarials, antihistamines, antidepressants) or lead to hypokalaemia (e.g. certain diuretics) should be avoided [37].

2.4.3 PHARMACOKINETICS

2.4.3.1 ABSORPTION

The absorption of oral doses appeared to be relatively rapid, as the highest blood concentrations of the drug were measured 0.5-3 hours after the dose (mean value 1.4 hours) [43], in the study performed in rats. The blood levels of levomepromazine that were observed in the study of [redacted] were in accordance with previously reported blood levels after intravenous administration of this drug in the rat [44]. Relative rapid absorption of levomepromazine after oral administration was evidenced by the onset of sedation in 10 to 15 minutes and by the rate of disappearance of the drug from the gastrointestinal tract [44].

The pharmacokinetic parameters of levomepromazine after oral or intra-arterial administration in rats are presented in Table IX.

Table IX Body weight of the animals and pharmacokinetic parameters of levomepromazine. F: extent of systemic availability.$t_{1/2}$: biological half-life. V_B: apparent volume of distribution. Cl: total body clearance.[43]

Animal number	Body weight (g)	Route of administration	F (%)	$T_{1/2}$ (hrs)	Vβ (L/kg)	Cl (ml/min)
1	525	o (5), i.a. (5)	73	11.6	53.0	28.5
2	372	o (4), i.a. (5)	14	4.7	7.6	7.0
3	279	o (2), i.a. (5)	3	4.7	3.6	2.5
4	288	o (3), i.a. (4)	27	5.2	7.8	5.2
5	299	o (3), i.a. (2)	22	9.0	26.7	10.5
6	429	o (2)		4.0		
7	359	0 (3)		15.9		
8	358	o (2)		2.7		
9	422	o				
10	446	i.a. (2)		1.7	7.1	21.4
11	281	i.a. (2)		1.5	4.5	9.1
12	310	i.a. (3)		6.0	22.1	13.2
Mean value	**364**		**28**	**6.1**	**16.6**	**12.3**

(a) o: oral; i.a.: intraarterial. The number of points used in the calculation of $t_{1/2}$ are given in parentheses.
(b) The mean value of $t_{1/2}$ from two experiments are given for animal no. 1-5.

2.4.3.2 DISTRIBUTION

In the study of [redacted], the pharmacokinetic profile of levomepromazine in rats was investigated after oral and parenteral administration [43]. The apparent volume of distribution of levomepromazine was relatively large in the rat (16.6 L/kg), although apparently smaller than the values in man (20-

40 L/kg) that have been reported [45].The distribution phase was characterized by a rapid decline of the levomepromazine concentrations, and lasted for about 8 hours after the infusion period [43].

The studies on the organ distribution of levomepromazine in the rat [44] indicate that there is also rapid uptake of the drug by organ depots, especially parenchymatous tissues, and this is consistent with findings on most basic compounds. In the case of methotrimeprazine, organ levels of the drug may still be appreciable 12 hr. after its administration. The highest drug concentration was found in the lungs. Appreciable concentrations were also found in the brain and kidneys. Lower concentrations were found in the gastrointestinal tract, liver and muscle and very low concentrations were found in the blood [44].

The regional distribution of levomepromazine and its metabolite desmethyl-levomepromazine in human brain tissue was demonstrated by [redacted] The drugs appeared to accumulate in brain tissue relative to blood and there was a region-specific distribution of levomepromazine with high values in basal ganglia [46].

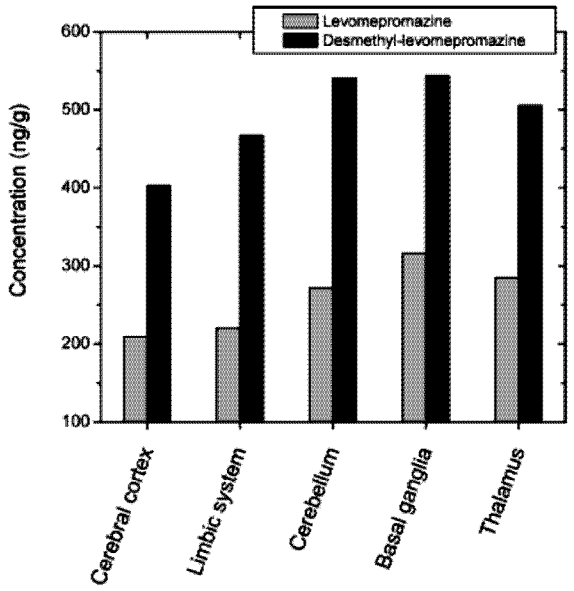


Figure 5 Regional distribution of levomepromazine and desmethyl-levomepromazine in human brain tissue [46]

2.4.3.3 METABOLISM

Levomepromazine sulfoxide and N-monodesmethyl levomepromazine are the two major non-polar metabolites of the drug in man [47]. In studies of their binding affinity to central a-adrenergic and dopaminergic receptors in the rat, N-monodesmethyl levomepromazine was active and had a 20-30 % lower potency than levomepromazine itself [48]. Levomepromazine sulfoxide was, on the other hand, virtually inactive in the dopamine receptor binding test but had 25 % of the potency of levomepromazine in the a-adrenergic receptor binding test.

The first pass metabolism of levomepromazine was investigated by [redacted] by measuring the blood levels of the drug and two of its metabolites in the rat after oral and parenteral administration

[43]. The results were consistent with previously reported levels after intravenous administration of this drug in the rat [44].

A scheme of the metabolic pathway of levomepromazine is shown in Figure 6.

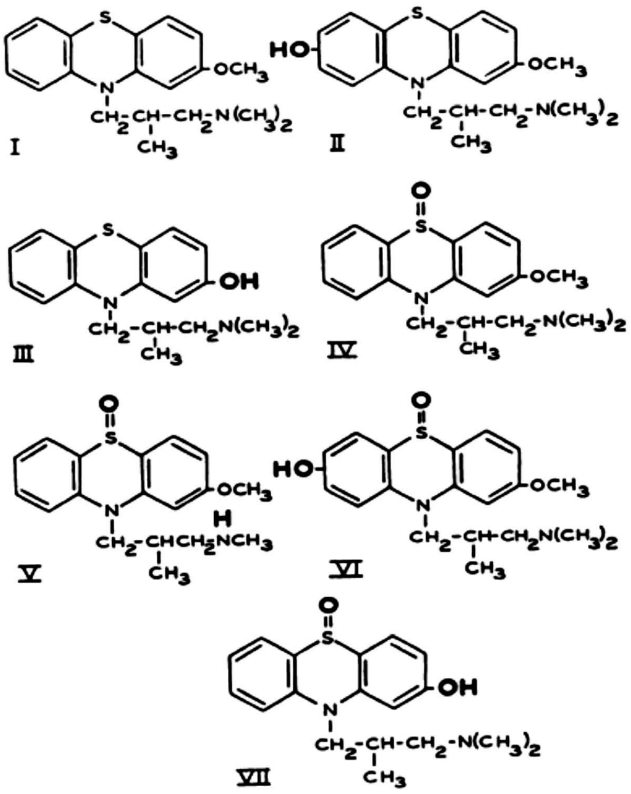


Figure 6 Metabolites of levomepromazine [44]

Levomepromazine (I) can undergo hydroxylation (II) and/or 0-demethylation (III) to yield the corresponding phenolic metabolites. These metabolites are then excreted either in the free form or as glucuronic acid conjugates. Simultaneous with these reactions sulfoxidation may occur. Since levomepromazine sulfoxide (IV) is not detectable in the urine, it may not be a stable metabolite and more likely it is rapidly metabolized after its formation to other products. Mono-desmethyhnethotrimeprazine sulfoxide (V) has been tentatively identified as a metabolite after the administration of either levomepromazine or levomepromazine sulfoxide. It was difficult to establish whether this metabolite is formed by N-demethylation of levomepromazine sulfoxide (IV) or by oxidation of mono-desmethyl-methotrimeprazine, since neither of the two likely precursors was detectable in the rat urine. However, it seems more likely that the metabolite (V) is formed by N-demethylation of methotrimeprazine sulfoxide, since it was one of the products identified after administration of methotrimeprazine sulfoxide. The pathway for the formation of the phenolic sulfoxides VI and VII also has two possibilities. They can be the products of either hydroxylation or O-demethylation of compounds II and III after sulfoxidation, or the sulfoxides can be formed after hydroxyl formation. However, judging from the number of conjugated products formed, the phenolic compounds are more likely to be conjugated with glucuronic acid than oxidized to the corresponding sulfoxide. This would favour sulfoxidation preceding hydroxyl formation but does not exclude the reverse from occurring [44].

The CYPs involved in the 5-sulfoxidation and N-demethylation of levomepromazine in human liver were identified by Wojcikowski et al. the results showed that CYP3A4 is the main isoform responsible for levomepromazine 5-sulfoxidation and N-demethylation at a therapeutic concentration of the drug [49]. Moreover, CYP1A2 substantially contributes to levomepromazine 5-sulfoxidation. At a higher, non-therapeutic concentration of the drug (100 mM), the contribution of CYP1A2 to levomepromazine metabolism noticeably increases compared to 10 mM levomepromazine, mostly at the expense of CYP3A4.

Table X Estimation of the contribution of CYP isoforms (CYPs) to the particular metabolic pathways of levomepromazine

CYPs	Relative contribution of the isoform to the total CYP contents in liver microsomes [fraction]	Relative contribution of the isoform to levomepromazine metabolism in liver microsomes [percentage]			
		Levomepromazine 5-sulfoxidation		Levomepromazine N-demethylation	
		10 µM	100 µM	10 µM	100 µM
CYP1A2	0.127	20.3	28.5	7.9	31.9
CYP2A6	0.040	0.6	0.4	0.1	0.5
CYP2B6	0.002	0.2	0.2	0.4	0.3
CYP2C8	0.065	2.0	1.3	3.0	1.4
CYP2C9	0.197	2.6	3.8	2.2	7.1
CYP2C19	0.038	0.7	4.6	8.0	9.7
CYP2D6	0.015	0.6	0.9	0.3	1.0
CYP2E1	0.066	1.1	1.3	0.1	0.6
CYP3A4	0.288	71.9	59.0	78.0	47.5

2.4.3.4 EXCRETION

As demonstrated by [redacted] less than 1 % of an intravenous dose of levomepromazine is excreted as unchanged drug in the urine by the rat, and it may, therefore, be assumed that the total clearance of the drug is virtually equal to its metabolic clearance in the rat [44]. Half-life of levomepromazine was measured to be 68 minutes [44]. After intravenous administration of 15 mg/kg, levomepromazine was detected in the urine as early as 30 minutes, but the total amount excreted during a 4-hour period was less than 1 % of the dose. With oral administration of 30 mg/kg of levomepromazine, the amounts excreted at the corresponding intervals were even less than those excreted after intravenous administration [44].

2.4.3.5 PHARMACOKINETIC DRUG INTERACTIONS

2.4.3.5.1 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 [50].

Concomitant administration of drugs known to inhibit hepatic metabolism of levomepromazine, might lead to enhanced therapeutic effects of levomepromazine [51].

2.4.3.5.2 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) [51].

Concomitant use of levomepromazine may affect the metabolism of phenytoin, resulting in toxic plasma concentrations of phenytoin [52].

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 [53].

2.4.3.5.3 Other drug interactions

The combined use of levomepromazine and propranolol may result to increased levels of both drugs [54]. The absorption of other drug substances can be affected by the inhibition of gastrointestinal motility.

2.4.3.6 OTHER PHARMACOKINETIC STUDIES

Other pharmacokinetic studies for levomepromazine were not identified in the public domain. However, the study of [redacted] demonstrated that N-demethylation of some phenothiazines, such as promazine, perazine and thioridazine is catalyzed by the isoenzymes CYP2D1, CYP2B2 and CYP1A2 in the rats (CYP1A2 does not refer to promazine). The 5-sulfoxidation of these drugs may be mediated by different isoenzymes e.g. CYP2D1 (promazine and perazine), CYP2B2 (perazine) or CYP1A2 (thioridazine). Isoenzymes belonging to the subfamilies CYP2C and CYP3A do not seem to be involved in the metabolism of the investigated neuroleptics in the rat [55].

[redacted] investigated the influence of classic and atypical neuroleptics on the activity of cytochrome P450 2C11 (CYP2C11), measured as a rate of testosterone 2α- and 16α-hydroxylation. The reaction was studied in control liver microsomes in the presence of neuroleptics, as well as in the microsomes of rats treated intraperitoneally (ip) with pharmacological doses of the drugs (promazine, levomepromazine, thioridazine and perazine 10 mg/kg; chlorpromazine 3 mg/kg; haloperidol 0.3 mg/kg; risperidone 0.1 mg/kg; sertindole 0.05 mg/kg) for one day or two weeks (twice a day), in the absence of the neuroleptics in vitro. Of the neuroleptics studied, only chronic treatment with levomepromazine, perazine and thioridazine diminished CYP2C11 activity and those effects were positively correlated with the observed decreases in the protein level of the enzyme [56].

2.4.4 TOXICOLOGY

2.4.4.1 SINGLE-DOSE TOXICITY

The reported toxicity doses of levomepromazine and levomepromazine hydrochloride after oral, intraperitoneal, intravenous and subcutaneous single administration are presented in Table XI and Table XII.

Table XI Reported toxicity values for levomepromazine [57]

Organism	Test type	Route	Reported Dose (normalized dose)	Effect
Bird - wild	LD_{50}	Oral	100 mg/kg (100 mg/kg)	-
Man	LD_{50}	Oral	7143 ug/kg (7.143 mg/kg)	Blood: Thrombocytopenia
Mouse	LD_{50}	Intraperitoneal	58500u g/kg (58.5 mg/kg)	-
Mouse	LD_{50}	Intravenous	39 mg/kg (39 mg/kg)	-
Mouse	LD_{50}	Oral	370 mg/kg (370 mg/kg)	-
Mouse	LD_{50}	Subcutaneous	300 mg/kg (300 mg/kg)	-
Rat	LD_{50}	Oral	1100 mg/kg (1100 mg/kg)	-
Rat	LD_{50}	Subcutaneous	45 mg/kg (45 mg/kg)	-

Table XII Reported toxicity values for levomepromazine hydrochloride [58, 59]

Organism	Test type	Route	Reported Dose (normalized dose)	Effect
Mouse	LD_{50}	Oral	380 mg/kg (380 mg/kg)	-
Mouse	LD_{50}	Intraperitoneal	135 mg/kg (135 mg/kg)	-
Mouse	LD_{50}	Subcutaneous	360 mg/kg (360 mg/kg)	-
Mouse	LD_{50}	Intravenous	75 mg/kg (75 mg/kg)	Behavioural: sleep

2.4.4.2 REPEAT-DOSE TOXICITY

No repeat dose toxicity studies have been conducted for Levomepromazine. However, when phenothiazine was administered to New Hampshire chicks, [week 0 - 4, 1400 mg/kg feed (7 mmol/kg); week 5-29, 2300 mg/kg feed (11 mmol/kg)], it was observed that weight gain was significantly depressed during week 0-7, but returned to control levels during week 8-29 [60].

2.4.4.3 GENOTOXICITY

2.4.4.3.1 In vitro

Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptic drugs. Although an increase in mammary neoplasms has been found in rodents following long-term administration of prolactin-stimulating antipsychotic agents, no clinical or epidemiologic studies conducted to date have shown an association between long-term administration of these drugs and mammary tumorigenesis in humans [19].

The mutagenic effects of levomepromazine have not been studied. However, the national toxicology programme reported no mutagenic effects of phenothiazines. Of the 10 phenothiazine derivatives tested, only those that had a chlorine substituent (chlorophenothiazine, chlorpromazine, compazine, and perphenazine) were photo-activated mutagens (NTP) [61].

In contrast to the psychotropic preparations, information on the biological activities of phenothiazines and their related compounds is limited. The interactions of phenothiazines with DNA, their antitumor activity, the differentiation or apoptosis-inducing activity, the tumour necrosis factor (TNF)-induction,

the anti-proliferative activity, the radical scavenging activity, the anti-mutagenic activity, the anti-plasmid activity, the antibacterial activity, the reversal of multidrug resistance (MDR) and blast transformation activity of phenothiazines have been reviewed by [redacted] [62].

Among fourteen phenothiazines, phenothiazine showed the low cytotoxic activity against human promyelocytic leukaemia cells, but most efficiently induced the differentiation of human myelogenous leukemic cell lines (ML-1, U-937, THP-1) into maturing monocytes/macrophages and internucleosomal DNA fragmentation in HL-60 cells (Table XIII). Perazine dimaleate showed DNA fragmentation-inducing activity, but did not induce the monocytic differentiation. Other phenothiazines of levomepromazine hydrochloride, 2-chlorophenothiazine, trifluoperazine dihydrochloride, methotrimeprazine maleate, perphenazine dimalate, chloropromazine hydrochloride, ethopromazine hydrochloride, promethazine hydrochloride, fluophenazine dimaleate, 10-methylphenothiazine, 10-ethylphenothiazine and 2-chloro-5-oxo-5H-phenothiazine did not induce monocytic differentiation nor DNA fragmentation. Electron spin resonance (ESR) spectroscopy showed that all phenothiazines did not produce radical.

Table XIII Differentiation-inducing Activity and Radical Intensity of Phenothiazines [62]

Compound	Cytotoxic activity (CC_{50}) (µM)	Differentiation inducing activity (%)	DNA fragmentation inducing activity	Radical intensity (at pH 12.5)
Phenothiazine	> 2010	14	+	< 0.02
Perazine Dimalate	11	0	+	< 0.02
Levomepromazine Hydrochloride	3	0	-	< 0.02
2-Chlorophenothiazine	> 1709	0	-	< 0.02
Trifluoperazine Dihydrochloride	15	0	-	< 0.02
Methotrimeprazine Maleate	9	0	-	< 0.02
Perphenazine Dimalate	13	0	-	< 0.02
Chlorpromazine Hydrochloride	14	0	-	< 0.02
Ethopromazine Hydrochloride	57	0	-	< 0.02
Promethazine Hydrochloride	16	0	-	n.d.[a]
Fluophenazine Dimaleate	x[b]	0	-	< 0.02
10-Methylphenothiazine	x[b]	0.3	-	< 0.02
10-Ethylphenothiazine	x[b]	4.5	-	< 0.02
2-Chloro-5-oxo-5H-phenothiazine	463	0.3	-	< 0.02

a: n.d: not determined
b: x: unknown

An in vitro assay was used in order to evaluate the possible genotoxicity effects of anti-psychotics, such as levomepromazine, was performed by [redacted] . As presented in the following figure, the authors concluded that these drugs did not induce DNA damage (ANOVA test; F= 0.789; P= 0.425) [63].

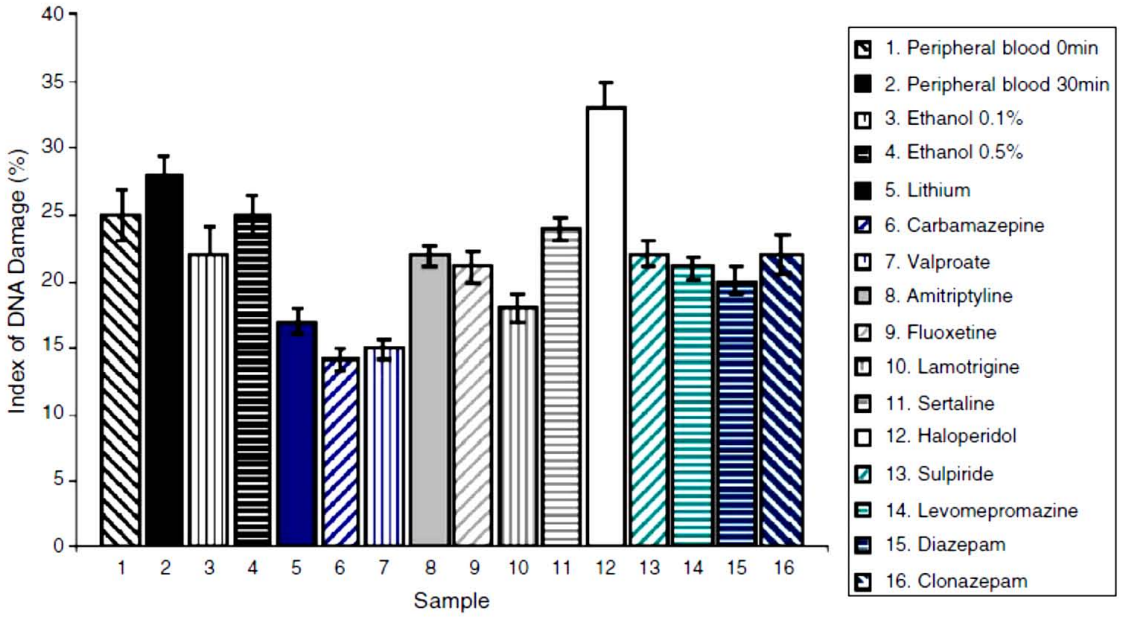


Figure 7 DNA Damage Index by drugs in peripheral blood

According to Figure 7, the studied drugs did not induce DNA damage.

2.4.4.3.2 In vivo

In vivo genotoxicity studies have not been performed for levomepromazine.

2.4.4.4 CARCINOGENICITY

2.4.4.4.1 Long-term studies

There is evidence in long-term mouse studies that phenothiazine can induce breast tumours. Breast tumours might result from increased blood prolactin levels [64]. Many neuroleptics also induce hyperprolactinemia in man [64].

2.4.4.4.2 Short- or medium-term studies

The effects of phenothiazines (at clinically relevant doses) on the viability and proliferation of leukemic cell lines and normal lymphocytes have been investigated by [redacted] Phenothiazines with different chemical structure and hydrophobicity were used: chlorpromazine, levomepromazine, promethazine, trifluoperazine, thioridazine. Interestingly, these compounds inhibited DNA polymerase activity in protein extracts obtained from mitochondrial fractions of leukemic cells and the results of the study support the suppression of proliferation and apoptosis induction in cultured leukemic cells without any effects on the viability of the normal lymphocytes [65].

Table XIV Phenothiazine concentrations causing a 50 % decrease in cell viability (CI_{50}) [65]

Cell line origin	Cell line	CI_{50} (µmol/l)				
		Trifluoperazine	Chlorpromazine	Thioridazine	Prometazine	levomepromazine
Normal lymphocytes		> 40	> 40	> 40	> 40	> 40
Burkitt's lymphoma	Raji	6.59	6.95	11.95	13.46	13.90
	Daudi	10.00	14.89	15.30	22.45	23.67
Chronic myelogenous leukemia	K562	9.49	12.04	13.88	14.57	19.18
B-acute lymphoblastic leukemia	BALL-1	11.90	11.19	15.00	14.28	31.71
T-acute lymphoblastic leukemia	MOLT-4	3.57	6.57	9.09	13.37	12.57
	CCRF-HSB-2	12.38	11.81	15.02	14.71	20.00
	HPB-ALL	13.57	12.33	14.76	15.24	28.57

2.4.4.4.3 Other studies

In vitro studies suggest that phenothiazines may have anti-cancer properties, whereas rodent studies suggest that some antipsychotics including phenothiazines, may increase the risk for certain cancers (mammary and pituitary tumours among female rodents, liver, pancreas and thyroid tumours among both genders of rodents), however levomepromazine is not listed in the studied antipsychotics that induce carcinogenicity [66]. [redacted] reported that based on the biological activity of thioridazine, such as interference with membrane function, DNA repair, signaling pathways, cell cycle, apoptosis induction, efflux inhibition and, also, its synergistic effect with doxorubicin, renders this phenothiazine a powerful anticancer drug and adjuvant in combined chemotherapy [67].

[redacted] evaluated several phenothiazine compounds and reported that levomepromazine was tested against sarcoma 180 and found to be active by showing also high potentiating effect on the activity of cyclophosphamide [68, 69]. In another study, although levomepromazine proved to be effective inhibitors of rhodamine 123 efflux of resistant mouse lymphoma and MDR/COLO 320 cells and modulated the intracellular drug accumulation in both resistant cell lines, it also exerted additional cytotoxic effects [70].

2.4.4.5 Reproductive and Developmental Toxicity

2.4.4.5.1 Fertility

Phenothiazines induce endocrine effects in the female rat, but do not affect the testes in the male. In the dog, phenothiazines cause low testicle weights, particularly at high dosage levels, but no morphological change is induced. The endocrine effects of these neuroleptics are probably attributable to effects on the hypothalamic nuclei [71]. However, studies confirming the same for levomepromazine are not available in the public domain.

2.4.4.5.2 Pregnancy

Animal studies are insufficient with respect to reproductive toxicity. In humans, the teratogenic risk of levomepromazine has not been evaluated. Different prospective epidemiological studies conducted with other phenothiazines have yielded contradictory results regarding teratogenic risk [72, 73].

Levomepromazine is not recommended during pregnancy and in women of childbearing potential not using contraception [72].

2.4.4.5.3 Lactation

Levomepromazine is excreted in breast milk in low amounts in human milk. A risk to the suckling child cannot be excluded. However, there are no literature data supporting any possible effects of levomepromazine during lactation.

2.4.4.5.4 Studies in Juvenile Animals

Toxicity studies in juvenile animals were not identified in the public domain.

2.4.4.6 LOCAL TOLERANCE

Not applicable since oral administration applies for Levomepromazine Oral Solution.

2.4.4.7 OTHER TOXICITY STUDIES

2.4.4.7.1 Antigenicity

Pre-clinical antigenicity studies for levomepromazine have not been identified in the public domain.

2.4.4.7.2 Immunotoxicity

No Immunotoxicity data for levomepromazine were found.

2.4.4.7.3 Mechanistic Studies

Mechanistic studies evaluating any toxic effects of levomepromazine were not identified in the public domain. One well-recognized property of phenothiazines is their ability to induce apoptosis in certain cell types [62, 74, 75]. Multiple studies on human and mouse cell lines have demonstrated the cytotoxic potential of phenothiazines given as monotherapy [62]. In addition, a few case reports exist that described anecdotal evidence for the antitumor activity of phenothiazines in vivo [76-78]. The study of [redacted] revealed the novel activity of phenothiazines as agents capable of inhibiting survival and inducing cell death in human small cell lung carcinoma (SCLC), a tumour type that is notoriously difficult to treat with conventional CT because of its ability to rapidly acquire resistance [79].

2.4.4.7.4 Dependence

Individuals with schizophrenia are at very high risk for drug abuse and addiction. A complementary hypothesis based on evidence showing that chronic exposure to antipsychotic medications can induce super-sensitivity within the brain's dopamine systems and that this in turn can enhance the rewarding and incentive motivational effects of drugs and reward cues was presented by [redacted] At the neurobiological level, these effects of antipsychotics are potentially linked to antipsychotic-induced

increases in the striatal levels of dopamine D2 receptors and D2 receptors in a high-affinity state for dopamine, particularly at postsynaptic sites. Antipsychotic-induced dopamine super-sensitivity and enhanced reward function are not inevitable consequences of prolonged antipsychotic treatment. At least two parameters appear to promote these effects; the use of antipsychotics of the typical class, and continuous rather than intermittent antipsychotic exposure, such that silencing of dopaminergic neurotransmission via D2/3 receptors is unremitting. Thus, by inducing forms of neural plasticity that facilitate the ability of drugs and reward cues to gain control over behaviour, some currently used treatment strategies with typical antipsychotics might contribute to compulsive drug seeking and drug taking behaviours in vulnerable schizophrenia patients [80].

Individual studies evaluating the potential of levomepromazine to induce dependence has not been evaluated in animal models of dependence.

2.4.4.7.5 Studies on Metabolites

As described in Section 2.4.3.3 (Metabolism) of the present document, the major metabolites of levomepromazine are levomepromazine sulfoxide and N-monodesmethyl-levomepromazine. Monodesmethyl levomepromazine [14] and levomepromazine sulfoxide [31] must be considered pharmacologically active.

The toxicological findings of levomepromazine content in the specimens of the examined case of [redacted] are presented below, suggesting that levomepromazine and its metabolites change significantly during the interval between death and autopsy and the direction of change appears to be dependent upon the site from which the specimens are sampled [81]. In this case, blood was collected for the first time 9 hours after death, and subsequently 31 hours after death, whereas the autopsy was performed 32-33 hours after death. The concentrations of levomepromazine in the studied autopsy material were within the range determined by other authors in fatal poisonings [82]. Fatal blood levomepromazine levels range from 0.8 to 8 mg/L, while in the liver the values are many times higher [83]. Other authors suggest that in cases of poisoning, levomepromazine metabolites may be present in higher concentrations than the precursor [84, 85], which was also confirmed by the study of [redacted] [81]. [redacted] assumed that the concentrations of levomepromazine sulfoxide and N-desmethyl-levomepromazine were generally higher than the concentrations of levomepromazine in poisoned psychiatric patients [85].

2.4.4.7.6 Studies on Impurities

[redacted]

2.4.4.7.6.1 *Justification of known impurities*

The release specification limit of all known impurities is based on the ICH Guideline Q3B (R2) "Impurities in new drug products". The maximum recommended dose of Levomepromazine HCl is 300 mg daily. [redacted]

Impurity B (Levomepromazine sulphoxide) is a major metabolite of Levomepromazine HCl. Numerous bibliographic data support this. According to [redacted] Levomepromazine sulphoxide and N-monodesmethyl levomepromazine are the two major non-polar metabolites of the drug in man [85]. It has also been reported that Levomepromazine sulfoxide is mainly formed by first-pass metabolism after oral doses of the drug in man but is not clear whether this process mainly takes place in the gut or in the liver. After repeated oral administration of the drug to patients, the concentration of Levomepromazine sulphoxide in plasma was 2 - 4 times higher than the concentration of unmetabolized Levomepromazine [31, 43, 86].

[redacted]

2.4.4.7.6.2 *Justification of unknown impurities*

The limit set for any unknown impurities is based on the ICH guideline; the maximum recommended dose of Levomepromazine HCl is 300 mg daily. [redacted]

2.4.4.7.6.3 *Justification of total impurities*

The limit set for total impurities is in accordance with batch release and stability data received [redacted].

2.4.4.7.7 Excipients

The product under assessment contains the following excipients:

- Propylene Glycol
- Glycerol
- Sodium Benzoate
- Saccharin Sodium
- Orange Flavour
- Hydrochloric Acid

The qualitative and quantitative composition of the proposed formulation is presented in Table XVI.

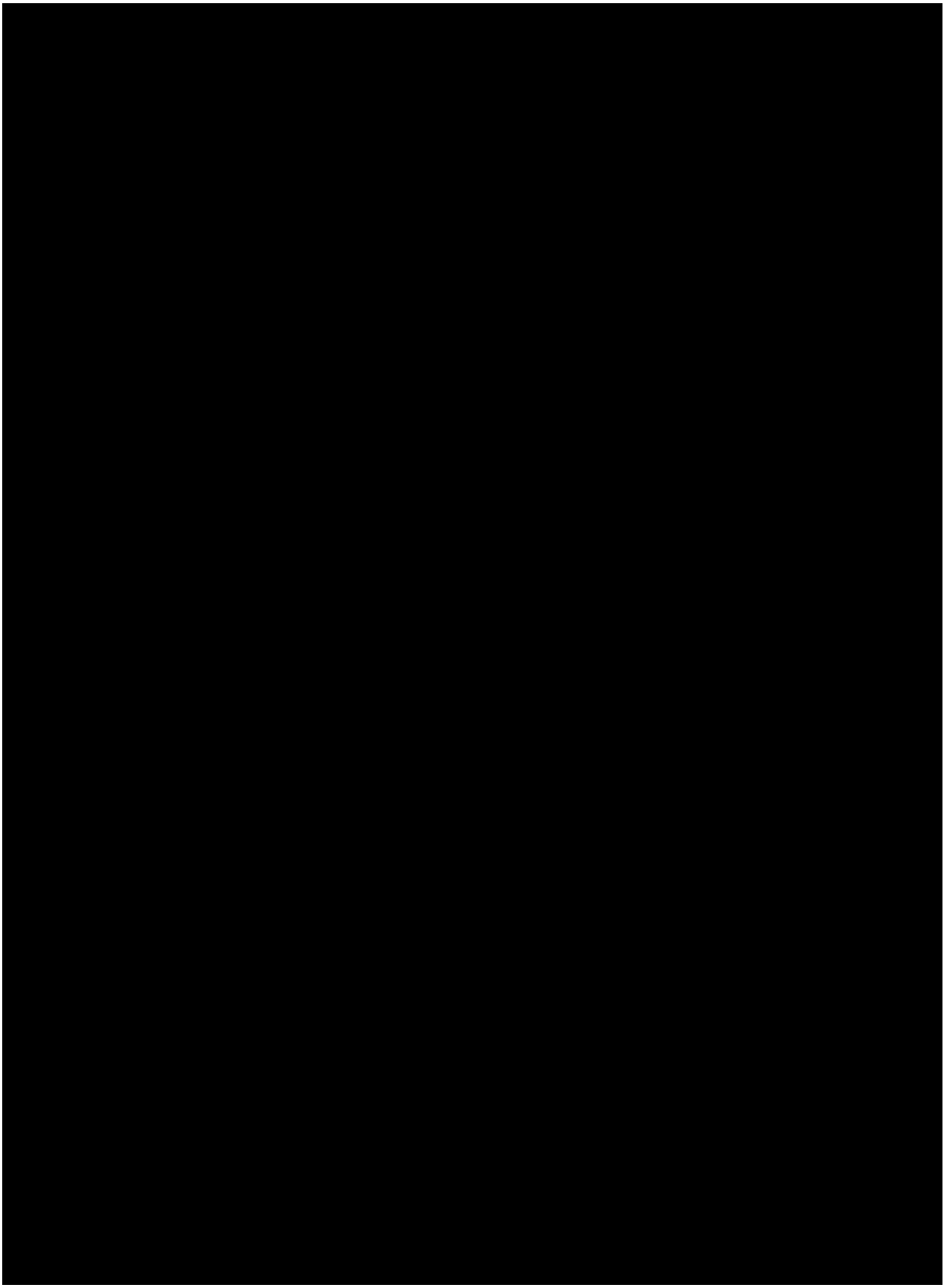
Table XVI Qualitative and quantitative composition of Levomepromazine 25 mg/5 ml Oral Solution

Ingredients	Quantity (mg)		
	1 ml	25 mg dose (5 ml)	300 mg (60 ml)
Propylene Glycol	[redacted]		
Glycerol			
Sodium Benzoate			
Saccharin Sodium			
Orange Flavour			
Hydrochloric Acid Sol. 1.0 N			
Purified Water			

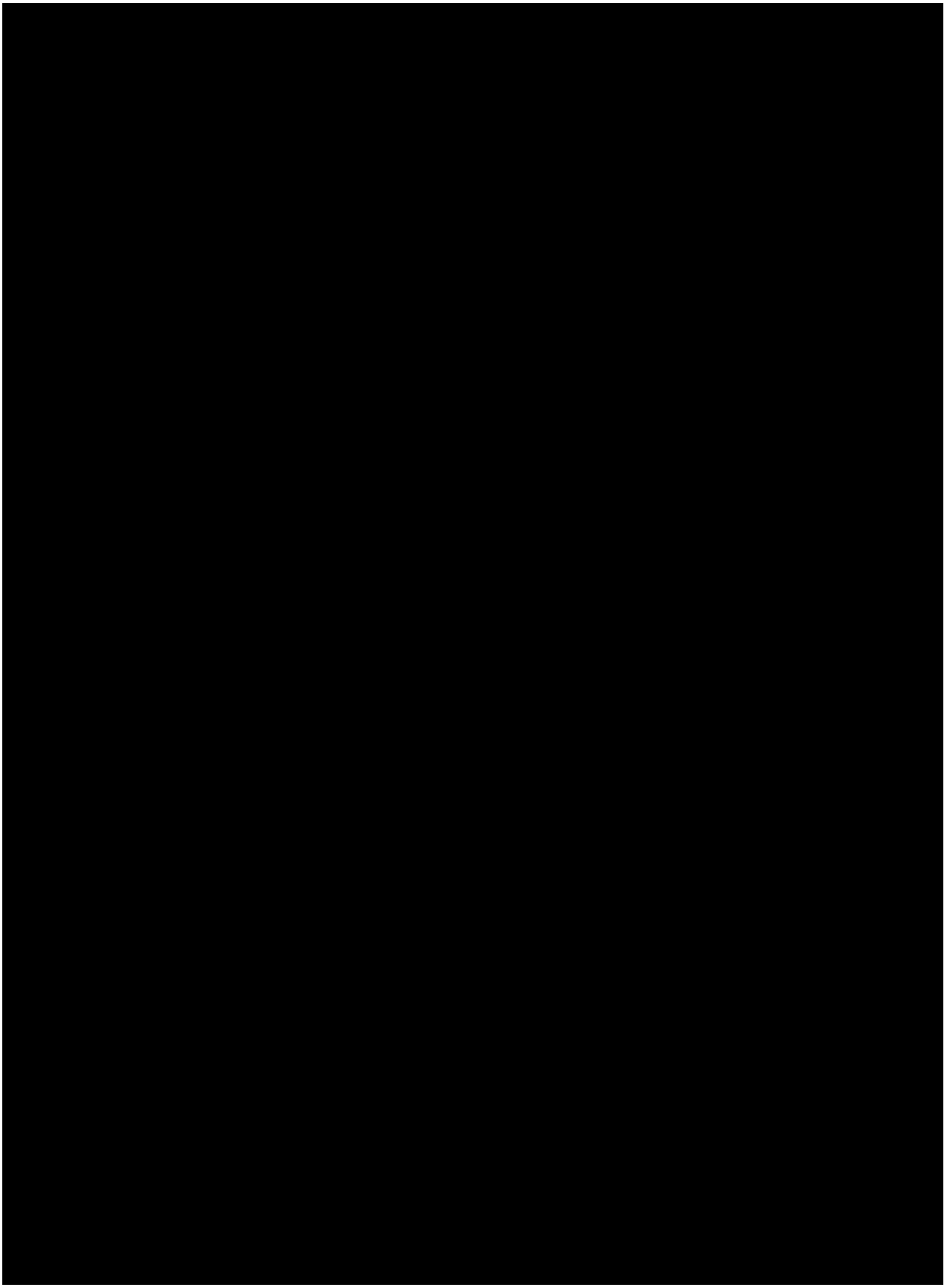
The pharmaceutical excipients are well known and commonly used in the pharmaceutical industry and fulfil the requirements of Ph. Eur or BP.

[redacted]

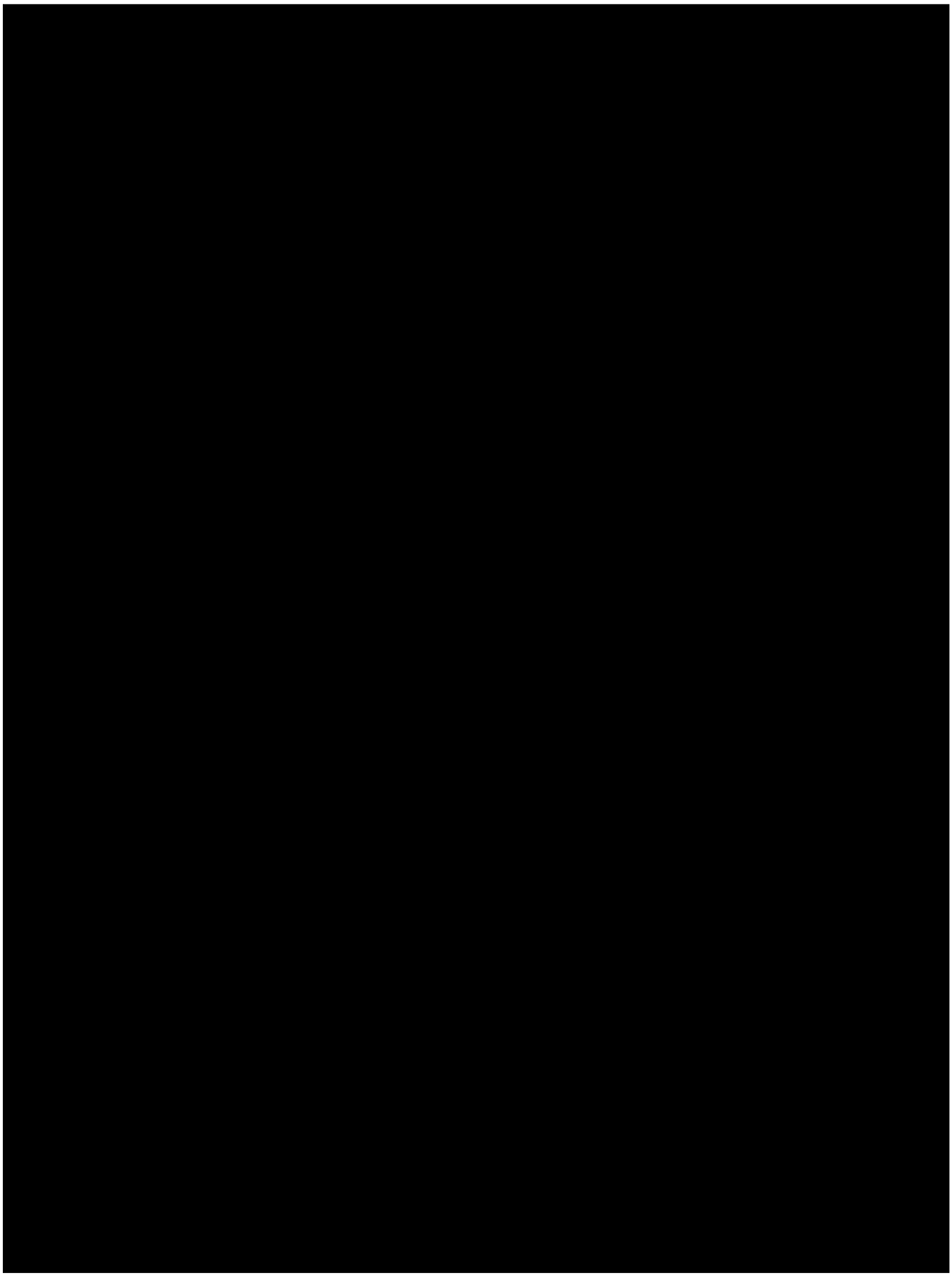
2.4 Nonclinical overview



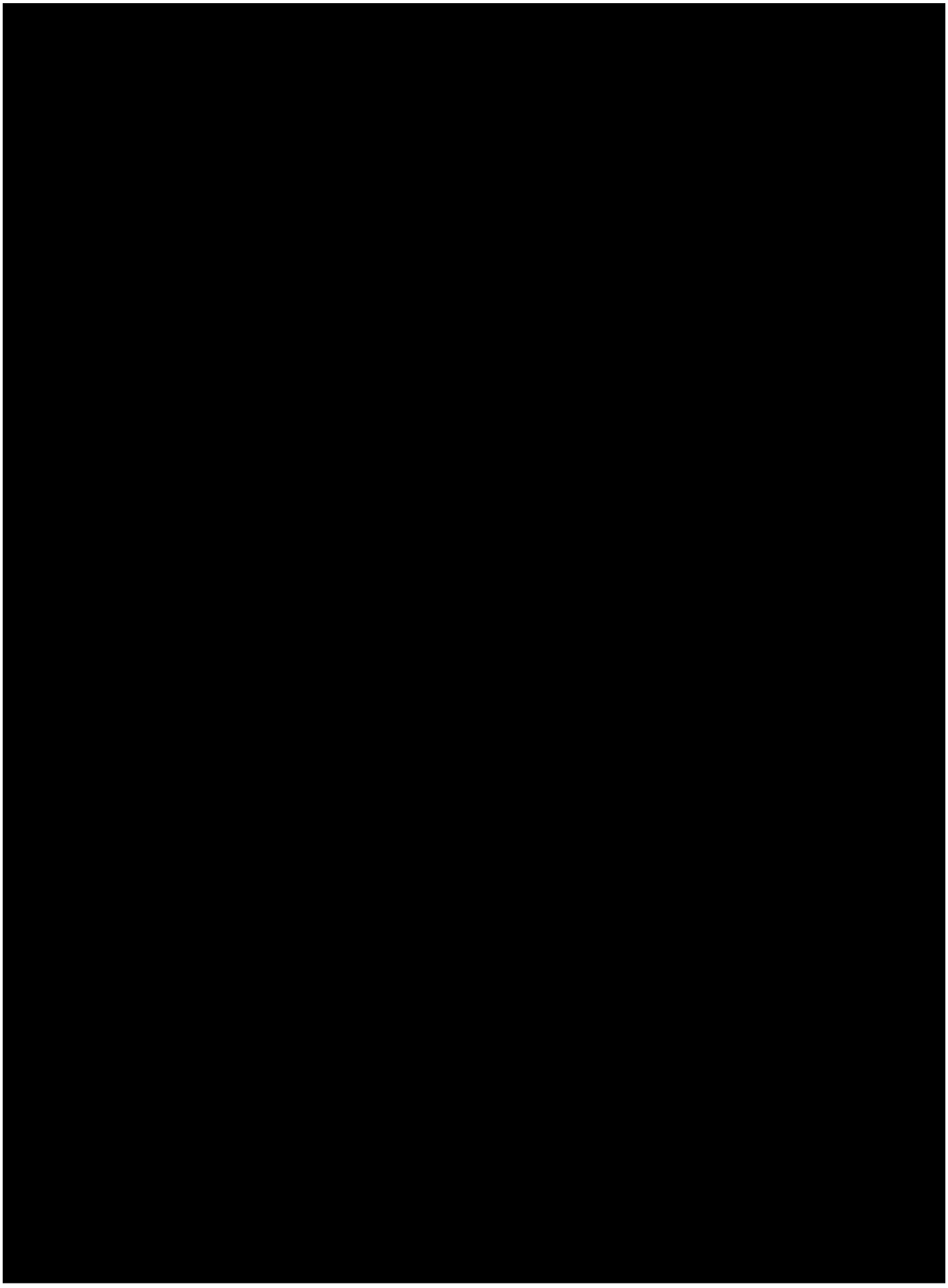
2.4 Nonclinical overview



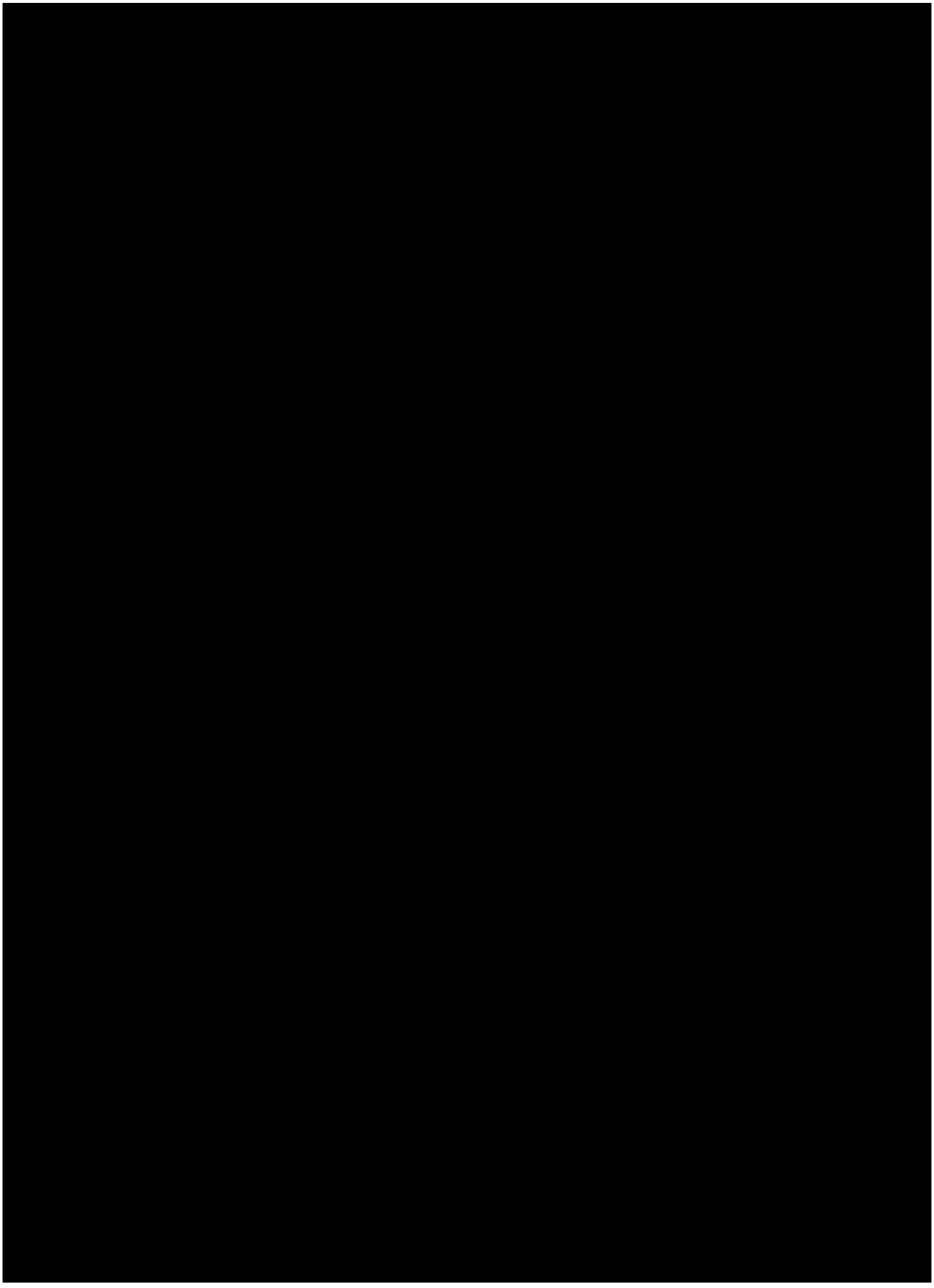
2.4 Nonclinical overview



2.4 Nonclinical overview



2.4 Nonclinical overview



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2.4.5 INTEGRATED OVERVIEW AND CONCLUSIONS

Levomepromazine is an aliphatic phenothiazine type of neuroleptic, chemically related to chlorpromazine and trifluorpromazine. Levomepromazine is binding to a large variety of receptors including dopamine, norepinephrine, serotonin, histamine and acetylcholine. In addition to its sedative and neuroleptic effects, it is a strong analgesic and is used frequently in palliative care.

The bioavailability of levomepromazine is about 50 % and this is attributed to a pre-systemic metabolism, where it is metabolised to the inactive levomepromazine sulfoxide.

The acute toxicity studies indicate that levomepromazine has a good safety profile. Repeated dose toxicity studies have not been conducted for levomepromazine. Levomepromazine did not also show any carcinogenic nor mutagenic properties. However, Levomepromazine is not recommended during pregnancy.

Levomepromazine has been categorized as class B drug (i.e. propensity of QTc prolongation), however the low-potency antipsychotic drugs such as levomepromazine and chlorpromazine have been reported to prolong the QTc interval only when given in high doses.

The most common adverse events after administration of levomepromazine are gastrointestinal disorders (dry mouth) and nervous system disorders (somnolence).

The proposed formulation is presented in the form of oral solution and the excipients used are well known and widely used in pharmaceutical preparations. The exposure to these excipients according to the maximum daily dose of the proposed product is considered safe.

The available preclinical information suggests that levomepromazine has a safety pharmacology and toxicity profile that will not preclude its clinical use according to the restrictions addressed in the SmPC. The characteristics of levomepromazine are adequately reflected in the SmPC and the indications and precautions for the use of this medicinal product are justified by its pharmacological properties.

2.4.6 LIST OF LITERATURE REFERENCES

[redacted]