2.4 Nonclinical Overview

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LIST OF ABBREVIATIONS

ADI	Acceptable Daily Intake
AIFA	Agenzia Italiana del Farmaco
API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
CNS	Central Nervous System
CP	Comparator Product
EFSA	European Food Safety Authority
EMA	European Medicines Agency
FDA	Food and Drug Administration
GI	Gastrointestinal
GMA	Global Marketing Authorization
GORD	Gastro-Oesophageal Reflux Disease
IL-4	Interleukin-4
IM	Intramuscular
IP	Intraperitoneal
I-R	Ischemia-Reperfusion
IV	Intravenous
LD_{50}	Lethal Dose
MHRA	Medicines and Healthcare products Regulatory Agency
MW	Molecular Weight
Ph. Eur	European Pharmacopoeia
RMP	Reference Medicinal Product
SC	Subcutaneous
SCF	Scientific Committee for Food
SmPC	Summary of Product Characteristics
SOS	Sucrose Octasulphate
TDLo	Lowest published Toxic Dose
TGF-β	Transforming Growth Factor β
WHO	World Health Organisation

2.4.1 OVERVIEW OF THE NONCLINICAL TESTING STRATEGY

This Nonclinical Overview examines the current state of scientific knowledge available on the general pharmaco-toxicological (nonclinical) properties of the active pharmaceutical ingredient (API) sucralfate and, in particular, the benefit-risk ratio in the intended indications of Sucralfate 1 g/5 ml Oral Suspension.

2.4.1.1 CHEMICAL CHARACTERIZATION

Sucralfate, an anionic, sulphated disaccharide, is an inhibitor of pepsin and an antiulcer agent. The drug is a basic, aluminum complex of sucrose sulphate. Sucralfate is structurally related to heparin but lacks anticoagulant activity. Sucralfate is also structurally related to sodium amylo-sulphate and chondroitin sulphate, but unlike these anionic sulphated polysaccharides, sucralfate is a pure disaccharide derivative. Although structurally related to sucrose, sucralfate is not utilized as a sugar in vivo in humans [1].

Sucralfate exhibits greater stability at the glycoside linkage than do most disaccharides or polysaccharides, apparently because of the presence of sulphate groups in sucralfate. Each of the 8 alcoholic hydroxyl groups of the disaccharide molecule are sulphated to yield sucrose octasulphate, and each of the sulphate ester anions forms a salt with an aluminum hydroxide group. Hydrogen bonds between hydroxyl groups and water molecules produce intramolecular and intermolecular bridges, forming a polymer [1].

Sucralfate occurs as a white, amorphous powder and is practically insoluble in water and in alcohol and soluble in strong acids and in alkalis [1].

2.4 Nonclinical overview

Table I: Chemical data and Identifiers of sucralfate

Chemical Data		
Name	Sucralfate	
Synonyms	Sucrose octakis(hydrogen sulfate) aluminum complex	
IUPAC Name	Hexadeca-μ-hydroxytetracosahydroxy[μ8-[1,3,4,6-tetra-O-sulfo-β-Dfructofuranosyl-α-D-glucopyranoside tetrakis(hydrogen sulfato)8-)]]hexadecaaluminum	
Chemical Formula	$C_{12}H_{54}Al_{16}O_{75}S_8$	
Mol. Mass	2086.67 $g \cdot mol^{-1}$	
Identifiers		
CAS number	54182-58-0	
ATC code	A02BX02	
ATC Groups	*1st Level*	A: Alimentary tract and metabolism
	2nd Level	A02: Drugs for acid related disorders
	3rd Level	A02B: Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)
	4th Level	A02BX: Other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)
PubChem	6398525	
DrugBank	DB00364	
ChemSpider	4911161	
UNII	XX73205DH5	
KEGG	C07314	
ChEMBL	ChEMBL611727	
ECHA InfoCard	100.053.636	

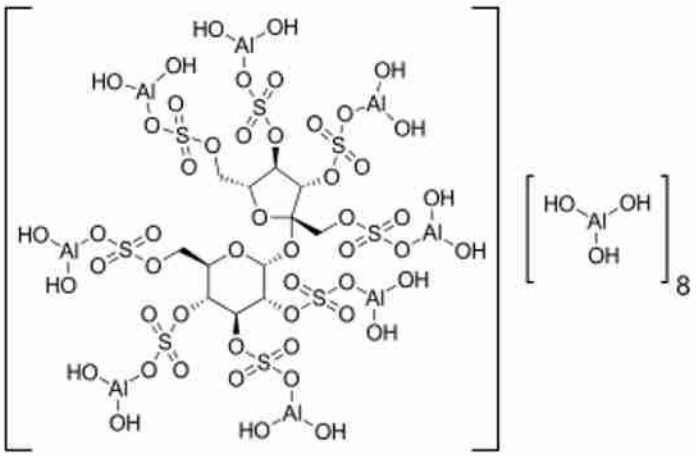


Figure 1: Chemical structure of sucralfate

2.4.1.2 SCIENTIFIC BACKGROUND AND REGULATORY STATUS

The current Application is submitted under Regulation 54 of the Human Medicines Regulations 2012, equivalent to Article 10a of Directive 2001/83/EC, i.e., well established use. Sucralfate has a well "established medicinal use" within the Community for at least ten years with recognized efficacy and an acceptable level of safety.

A full justification on the Legal basis of the present application is provided in Module 1.5.1.

The suitability of the regulatory strategy and the requirements for this application have been discussed in a scientific advice meeting with the MHRA [redacted] [2, 3].

Sucralfate was first introduced in Japan in 1968 by Chugai Pharmaceutical Co., Ltd. as a selective ulcer-protecting agent. Today, it is approved in over 30 countries. In 2019, Fuji Chemical Industries Co., Ltd. acquired the rights to sucralfate from Chugai. The active ingredient used in the development of Sucralfate 1 g/5 ml oral suspension was sourced from [redacted] ensuring that the product under evaluation contains the same API as the historic reference product, Antepsin.

In the UK the Reference Medicinal Product (RMP) was Antepsin 1 g/5 ml Oral Suspension (PL 12185/0010), originally licensed to Chugai Pharma UK Limited on October 12, 1998 [4]. This licence was withdrawn in 2019. A Freedom of Information request regarding the marketing authorisation of Antepsin confirmed that its authorisation was voluntarily withdrawn by the Marketing Authorisation Holder (MAH) on September 27, 2019 (https://www.gov.uk/government/publications/freedom-of-information-responses-from-the-mhra-week-commencing-20-september-2021/freedom-of-information-request-on-the-marketing-authorisations-for-antepsin-foi-211065). This withdrawal was due to commercial reasons rather than safety concerns.

Following its withdrawal from the UK market, the Italian version of Antepsin 1 g/5 ml Oral Suspension has been imported into the UK (PLPI 15814/1328). This product is manufactured by Laboratori Baldacci S.p.A. and repackaged by O.P.D. Laboratories Ltd., the Product Licence holder, under licence from Chugai/Fuji [5, 6].

The legal basis for the application has been selected in accordance with MHRA Guidance on Comparator Products in bioequivalence/therapeutic equivalence studies. In this case, representativeness between the non-UK Comparator Product (CP) and the UK Reference Medicinal Product (RMP) cannot be established, as the UK RMP is no longer available. Consequently, an alternative legal basis for submission, such as Regulations 54 (well-established use), has been considered. Given that the UK marketing authorisation for the reference product has been cancelled, the Comparator Product (CP) used for bridging in this application is the Italian version of Antepsin suspension (A.I.C. 022803047) [7], which is the same as the currently available on the UK market through parallel import.

The proposed indications for this product align with those of the withdrawn RMP, which includes treatment for duodenal and gastric ulcers and chronic gastritis in cases where standard treatments have failed, or symptoms persist. Additionally, this application includes extra indications based on the Italian Comparator Product used in the bridging studies, such as acute gastritis, NSAID-induced gastropathy, and reflux esophagitis. The posology of the suspension formulation remains consistent with Antepsin 1 g/5 ml Oral Suspension.

2.4.1.3 NONCLINICAL DEVELOPMENT PROGRAM

Since Sucralfate is a medicinal product the active substance of which has a 'well-established medicinal use' within the Community for at least ten years, with recognized efficacy and an acceptable level of safety it is possible to replace results of the pre-clinical and clinical trials by detailed references to published scientific literature (information available in the public domain). As a consequence, the non clinical overview only mirrors and summarizes the toxicological and pharmacological well-known properties of the active substance.

In order to bridge the literature data with the proposed pharmaceutical product the Applicant performed in vitro equivalence studies, in line with the draft US FDA guidance for sucralfate suspension (Draft Guidance on Sucralfate Suspension, February 2023) [8] and validated as a suitable approach during the scientific advice meeting with the MHRA (Advice number 3063). In this context, the Applicant conducted a comparison between the product under assessment and the Italian product, Antepsin 1 g/5 ml Oral Suspension (A.I.C. 022803047), which is the same as the one that is imported into the UK market (PLPI 15814/1328), through in vitro studies.

The results of the studies are summarised and discussed in Section 2.5.2.1 of the Module 2.5.

The full literature articles used during the compilation of the Nonclinical Overview are provided in Module 4.

2.4.1.4 SEARCH STRATEGY

[redacted]

- Date: beginning of database – 02 April 2025

[redacted]

2.4.2 PHARMACOLOGY

2.4.2.1 PRIMARY PHARMACODYNAMICS

2.4.2.1.1 Mechanism of action

Sucralfate acts locally, but it does not function as an antacid. Studies in normal volunteers have shown only minor variations in gastric pH after a 1 g dose. In animals, 2-5 % of an oral dose of radio-labelled drug is recovered in the urine; the balance is excreted in the feces [9].

The integrity of the protective sucralfate barrier is apparently not affected by food and antacid. In animal studies, sucralfate was found bound to ulcer tissue and sparsely distributed over normal tissue when antacid was given immediately after the drug. Also, the drug was found concentrated at the ulcer crater when animals ate to satiety one hour after drug administration.

The nature of this adherence or bonding has been studied. The viscous substance formed by sucralfate tablets in the gastrointestinal environment is made up of polyvalent anions, stemming from the sucrose sulphate moiety. According to the available data, ulcers have high concentrations of positively charged proteins as a result of transudation of interstitial fluid and exudation of exogenous serum albumin and perhaps of endogenous plasma proteins. Protein from damaged mucosal cells is also likely to be present in the ulcer crater. Experimental evidence has been provided to support his hypothesis that the binding of sucralfate to exposed tissue results from the electrical attraction between the negatively charged drug and the abundant supply of protein at the ulcer site.

Just how the adherent material encourages ulcer healing has been approached through studies of its actions against acid, pepsin, and bile acids. An in vitro study has demonstrated the capacity of sucralfate to protect albumin from the diffusion of acid. Albumin spread over a glass frit and used as a divider between two solutions of different pH, allowed the passage of acid solution within 30 minutes (Figure 2). Antacid added as a protective layer over the albumin delayed the passage only slightly longer. When the albumin-coated frit was covered with a layer of sucralfate the passage of the acid solution was delayed more than twice as long as with albumin or albumin-plus-antacid. Sucralfate did not appreciably affect the acidity of the solution.

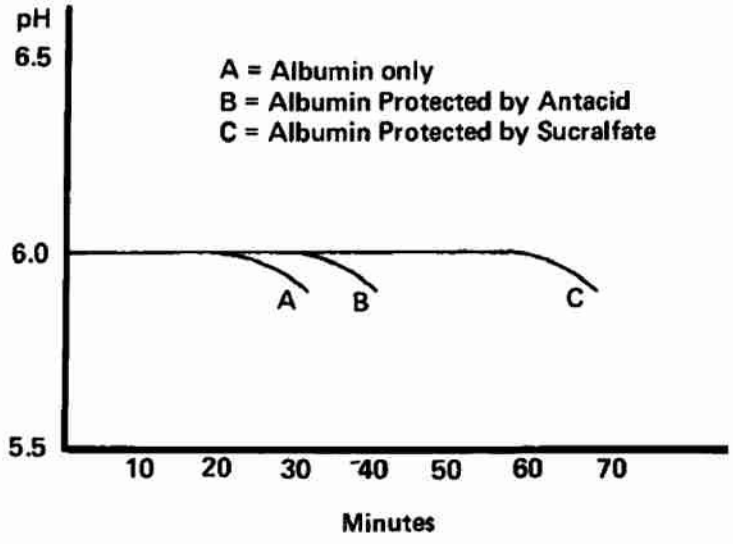


Figure 2 Comparison of sucralfate and antacid protection of albumin from acid [9]

A similar protective effect of sucralfate was demonstrated against pepsin. Used as a coating over albumin, sucralfate delayed the production of tyrosine (produced by pepsin breakdown of albumin) for a significant period of time, as shown in Figure 3.

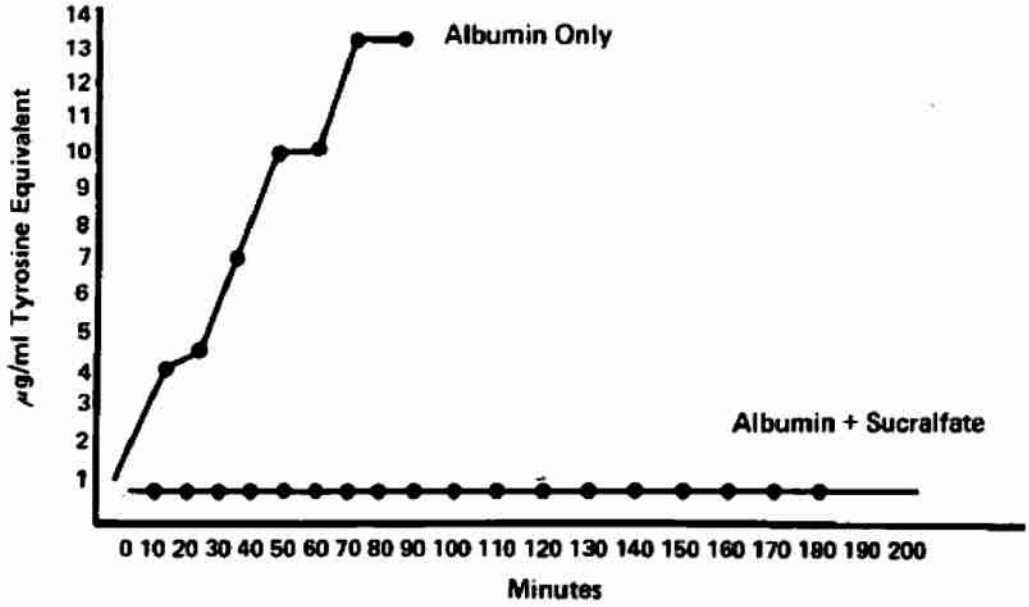


Figure 3 Breakdown of albumin by pepsin when unprotected and when protected by sucralfate [9]

The mechanisms of action of sucralfate are summarised in table below.

Table III Mechanism of action of sucralfate [10]

Adsorbs pepsin + bile acids
↑ Bicarbonate + mucus
↑ Alkaline gastric microclimate
↑ Prostaglandin secretion
↑ EGF mucosal concentration
Stimulates mucosal macrophages
Protects vascular integrity
Protects proliferative zone
Promotes epithelial restitution

2.4.2.1.2 In vitro studies

The oesophageal muco-retentive properties of sucralfate have been confirmed by in vitro models [11].

Several gastric irritants, including ethanol, hydrogen peroxide, and hydrochloric acid, induced both necrosis and apoptosis in cultured gastric mucosal cells. [redacted] demonstrated that the cytoprotective effect of sucralfate on gastric mucosa in vivo can be explained, at least in part, by its inhibitory effect on gastric irritant-induced necrosis [12].

2.4.2.1.3 In vivo studies

The investigations of [redacted] indicated that sucralfate can protect against acid injury in oesophagus by the diverse actions of its two major components, aluminum hydroxide and SOS. Aluminum hydroxide protects by neutralization of luminal H^+ and SOS protects by enhancement of mucosal defenses against H^+ diffusion and H^+-induced changes in epithelial permeability. Further, because the "barrier" aspects of sucralfate treatment are mimicked by the water- and acid-soluble SOS component, polymerization of sucralfate into a visible gum appears unnecessary to its action [13].

Table IV Effect of sucralfate on the changes in electrical parameters induced by luminal HCl (60 mM) in rabbit oesophageal epithelia [13]

Treatment group	n	Baseline (Ringer-exposed) PD	Baseline (Ringer-exposed) I_{sc}	Baseline (Ringer-exposed) R	HCl-exposed, 45 min PD	HCl-exposed, 45 min I_{sc}	HCl-exposed, 45 min R	Posttreatment, 60 min[a] PD	Posttreatment, 60 min[a] I_{sc}	Posttreatment, 60 min[a] R
Sucralfate (10 mg/ml, post-HCl)	5	−15 ± 1.8	11 ± 1.2	1367 ± 137	−15 ± 2.9	20 ± 5.1[b]	789 ± 111[b]	−9 ± 1.2[c]	7 ± 1.7[c,d]	1545 ± 362[c,d]
Controls	5	−16 ± 1.5	10 ± 1.2	1659 ± 187	−14 ± 1.5	16 ± 1.7[b]	834 ± 81[b]	−12 ± 1.4	16 ± 2.0	715 ± 67[c]

I_{sc}, short circuit current; PD, potential difference; R, electrical resistance. [a] Sucralfate added to luminal solution 45 min after the addition of HCl, between HCl-exposed and posttreatment periods. [b] $p < 0.05$ HCl-exposed vs. Ringer baseline for same treatment group. [c] $p < 0.05$ posttreatment vs. HCl-exposed for same treatment group. [d] $p < 0.05$ sucralfate vs. controls.

[redacted] investigated the mechanisms of gastroprotective action of sucralfate. Studies in vivo were conducted with groups of rats with and without indomethacin pretreatment, and the animals received sucralfate followed by ethanol. In the in vitro system, gastric mucosa was cultured in the presence of sucralfate with and without indomethacin [14]. The in vivo experiments revealed that ethanol caused extensive gastric lesions which were significantly reduced following sucralfate pretreatment. Furthermore, sucralfate was also capable of preventing the detrimental effect of indomethacin on gastric mucus gel dimension and its mucin content. The data with gastric mucosal culture showed that the sucralfate elicited increase in mucin was accompanied by the enhanced turnover of mucosal phosphoinositides. Regardless of the inclusion of indomethacin, sucralfate evoked 23 % reduction in phosphatidylinositol, 24 % increase in inositol-1-phosphate and 3.4-fold increase in inositol-1,4,5-trisphosphate, thus indicating the activation of phosphoinositide-specific phospholipase C.

Table V Effect of sucralfate on macroscopic necrosis of gastric mucosa elicited by ethanol [14]

Pretreatment	Necrosis % of total glandular area
Vehicle + ethanol	41.7 ± 5.3
Sucralfate + ethanol	3.9 ± 1.4*
Indomethacin + vehicle + ethanol	43.5 ± 4.2
Indomethacin + sucralfate + ethanol	7.2 ± 3.4*

Values represent the means ± SD of analyses performed on 8 animals in each group. *$P < 0.05$.

Table VI Effect of sucralfate on gastric mucus surface gel [14]

Treatment	Mucus (mg/100 mg)			Gel thickness μm
	Protein	Carbohydrate	Lipids	
Vehicle (0.9% NaCl)	67.4 ± 6.5	11.3 ± 1.7	19.4 ± 2.1	235 ± 29
Indomethacin + vehicle	75.8 ± 7.9	9.7 ± 1.0	11.9 ± 1.3	179 ± 20
Sucralfate	60.1 ± 6.6	14.9 ± 1.5*	20.7 ± 2.2	297 ± 33*
Indomethacin + sucralfate	65.3 ± 7.1	14.6 ± 1.5*	20.1 ± 2.3*	228 ± 24*

Values represent the means ± SD of analyses performed on 8 animals in each group. *The effects of sucralfate vs vehicle and indomethacin + sucralfate vs indomethacin + vehicle were significant at $*P < 0.05$.

Table VII Effect of sucralfate on gastric mucosal phosphatidylinositol turnover in the presence of indomethacin [14]

Component	% of total [^{3}H]inositol incorporation			
	Control	Sucralfate	Indomethacin	Indomethacin + sucralfate
PI	49.1 ± 6.1	37.6 ± 4.0*	51.4 ± 6.7	37.3 ± 3.9*
PIP	7.1 ± 0.9	8.2 ± 1.1	6.9 ± 0.9	8.0 ± 1.0
PIP_2	1.0 ± 0.2	1.0 ± 0.2	1.1 ± 0.2	1.2 ± 1.0
IP_1	26.2 ± 3.0	32.6 ± 3.3*	24.3 ± 3.1	33.0 ± 3.8*
IP_2	14.5 ± 1.2	13.4 ± 1.1	14.1 ± 1.1	13.5 ± 1.4
IP_3	2.1 ± 0.1	7.2 ± 0.9*	2.2 ± 0.3	7.0 ± 0.6*

Values represent the means ± SD of six separate experiments for each type of condition. The effects of sucralfate vs control and indomethacin + sucralfate vs indomethacin were significant at $*P < 0.05$. PI, phosphatidylinositol; PIP, phosphatidylinositol-4-phosphate; PIP_2, phosphatidylinositol-4,5-bisphosphate. IP_1, inositol-1-phosphate; IP_2, inositol-1,4-bisphosphate; IP_3, inositol-1,4,5-trisphosphate.

The results demonstrate that the gastric mucosal protective action of sucralfate is not mediated by endogenous prostaglandins, but appears to involve the metabolism of phosphoinositide-derived messenger molecules [14].

The effects of oral administration of sucralfate on gastric damage induced by I-R were investigated by [redacted] [15]. Sucralfate (1-100 mg/kg, 15 min before I-R) significantly reduced the total erosion area observed immediately after I-R. A high dose of sucralfate (30-100 mg/kg) inhibited the increase in the thiobarbituric acid-reactive substances, an index of lipid peroxidation, induced by I-R, although a low dose of it failed. When sucralfate (30 mg/kg, once a day) was orally administered after I-R, it prevented mucosal damage from developing into gastric ulcers: the total area of the ulcers was significantly reduced compared to that without sucralfate administration 72 h after I-R.

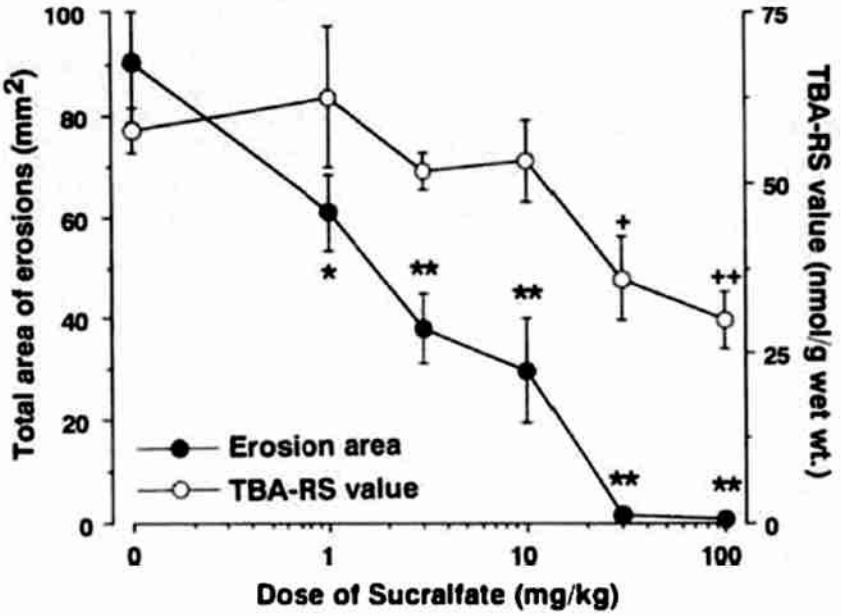


Figure 4 Dose-dependent effects of sucralfate on total area of erosions (•) and thiobarbituric acid- reactive substances (TBA-RS) value (O) in the gastric mucosa. Gastric mucosal injuries were produced by 1-R.

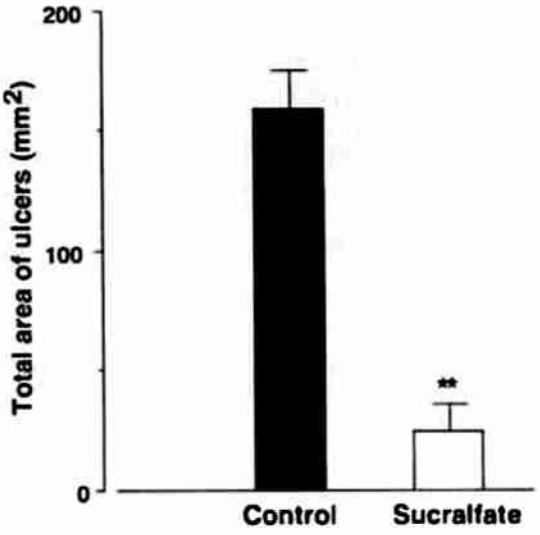


Figure 5 Effect of sucralfate on the gastric ulcers induced by I-R. Sucralfate (30 mg/kg once a day) was orally administered immediately and 24 and 48 h after I-R injury.

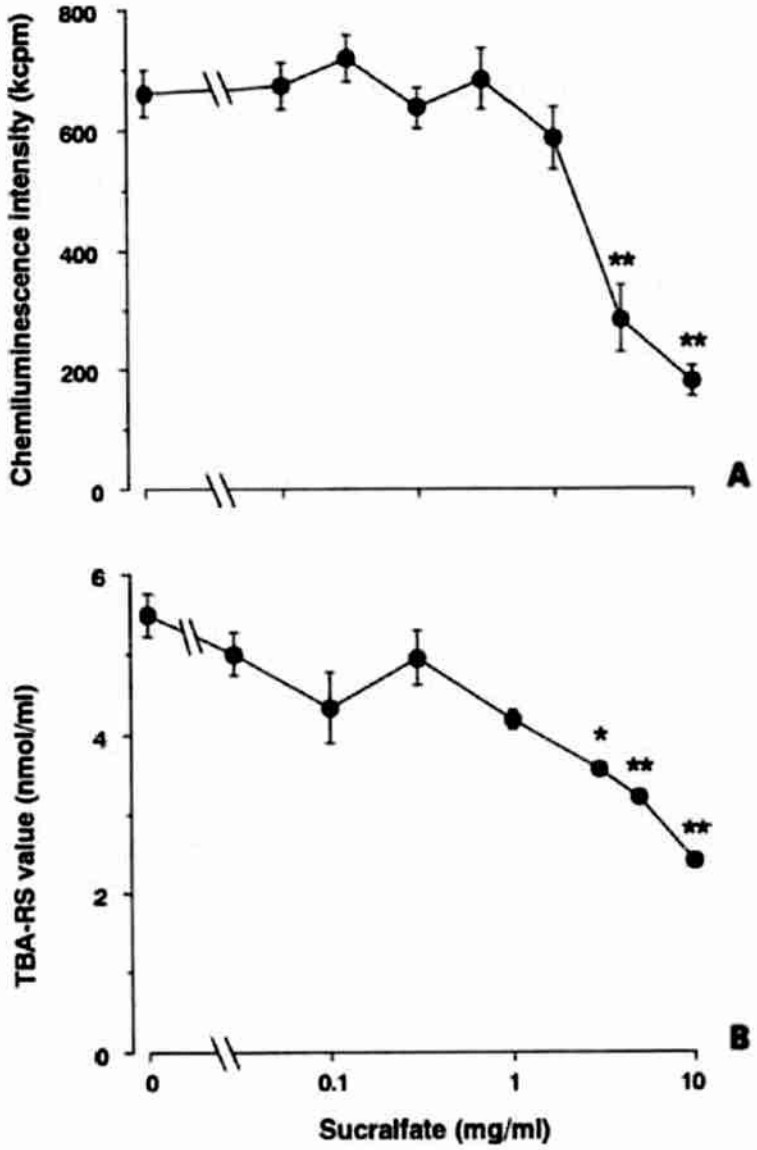


Figure 6 Effects of sucralfate on xanthine-xanthine oxidase-derived superoxide radicals (A) and hydroxyl radical-induced lipid peroxidation of human erythrocyte membrane ghosts (B) in vitro [15]

High concentrations of sucralfate (3-10 mg/ml) reduced the superoxide radicals generated by leukocytes or xanthine-xanthine oxidase, and protected erythrocyte membrane ghosts against lipid peroxidation induced by hydrogen peroxide and Fe^{2+} in vitro. These results indicated that sucralfate may prohibit both the generation of acute gastric mucosal injury and its progression to ulcer induced by I-R, probably due to a cytoprotective action on the mucosal surface [15].

2.4.2.1.4 Experimental Ulcer Models and Effect of Sucralfate on Acute Ulcer Models

2.4.2.1.4.1 *Pylorus-Ligated Ulcers*

The testing of the drug using this model [16] showed that the preventive effect of sucralfate on ulcers, as expressed in terms of a percentage of the ulcer index value for controls at 14 hr after ligation of the pylorus, was 60 % at 30 mg/kg, and above 90 % at 100 and 300 mg/kg (Figure 7). However, there were

no substantial differences in pepsin output between the control group, and the groups receiving 100 and 300 mg/kg of sucralfate.

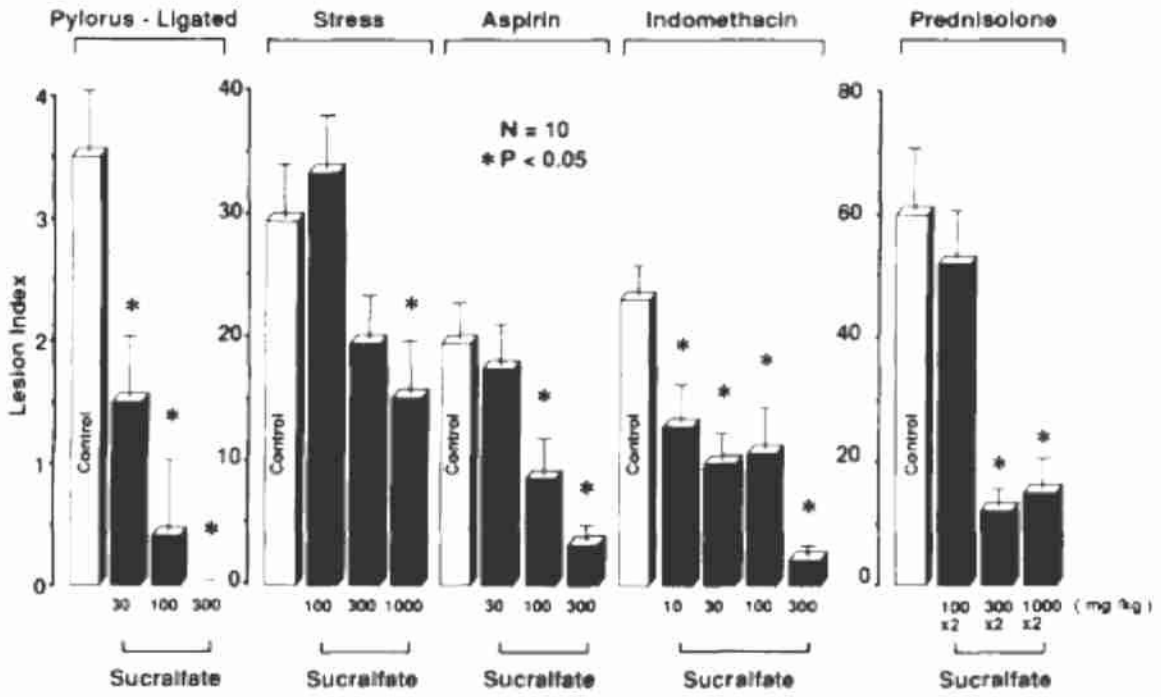


Figure 7 Effects of sucralfate on various acute gastric ulcers induced in rats. There was significant prevention of the development of gastric ulcers with sucralfate [17]

2.4.2.1.4.2 Stress Ulcers

Sucralfate at a dose of 1000 mg/kg had a significant (52 %) inhibitory effect, as compared with a control, on the superficial erosions of the gastric mucosa caused by 7-hr immersion in cold water (23°C), although the drug at 100 or 300 mg/kg failed to provide significant protection against this form of stress-induced mucosal damage. Increased gastric acid secretion, gastric hypermotility, and local circulatory disturbance occurring in association with excitation of the vagal nervous system have been implicated as the principal causes of stress ulcers. The beneficial effect of sucralfate on this particular type of experimental ulcer, like its effect on pylorus-ligated ulcers, seems to be the result of protection of the gastric mucosa against aggressive factors [17].

2.4.2.1.4.3 Drug-Induced Ulcers

Ulcers induced by 100 mg/kg aspirin in pylorus-ligated rats were inhibited in a dose-dependent fashion by pretreatment with sucralfate, with 84.8 % inhibition at a dose of 300 mg/kg. A similar dose-dependent antiulcer effect was produced by pretreatment of pylorus ligated rats with propantheline, antacids, or cimetidine (Figure 7).

Sucralfate was demonstrated to inhibit the development of indomethacin ulcers in a dose-dependent fashion.

It has been reported that pretreatment with sucralfate at 125 mg/rat proved effective in preventing gastric mucosal injury caused by exposure to 30 mM sodium taurocholate.

The effectiveness of sucralfate against ethanol ulcers has been established by Hollander et al [18], who demonstrated that pretreatment with sucralfate was effective in the prevention of ethanol ulcers.

2.4.2.1.4.4 *Acetic Acid Ulcers*

Using the acetic acid ulcer model with delayed ulcer healing caused by indomethacin, sucralfate was tested as to its potency in accelerating ulcer healing. The results indicated that the drug promoted the spontaneous healing of ulcers (Figure 8) [16, 19].

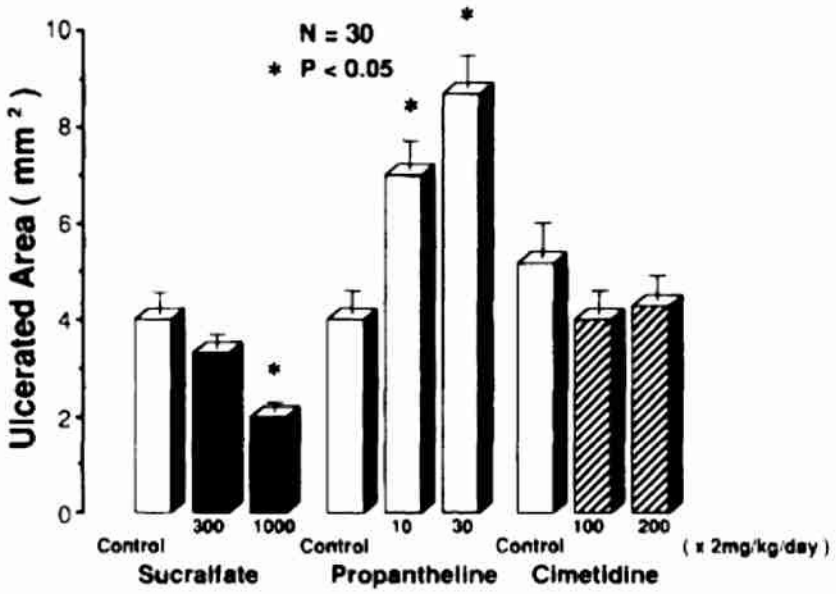


Figure 8 Effects of sucralfate, propantheline, and cimetidine on delayed healing of acetic acid-induced gastric ulcers in rats [17]

2.4.2.2 SECONDARY PHARMACODYNAMICS

The various effects of sucralfate are exerted at its contact sites in the stomach and duodenum. Considering that the binding of sucralfate at the ulcer crater is much stronger than the adhesion to the normal mucosa, it is postulated that those effects would be magnified at the ulcerated area. Thus, the actions of sucralfate seem to be divided into two groups: one is a group of local or site protective actions selectively directed to the ulcerated area and the second group consists of stimulation of mucosal defenses, i.e., cytoprotection. However, the difference between the two groups of actions is modulated by the strength of binding.

2.4.2.3 SAFETY PHARMACOLOGY

2.4.2.3.1 Central nervous system

CNS toxicity has not been reported for sucralfate in animal studies.

2.4.2.3.2 Cardiovascular system

Cardiovascular toxicity has not been reported for sucralfate.

2.4.2.3.3 Respiratory system

Respiratory toxicity has not been reported for sucralfate.

2.4.2.4 PHARMACODYNAMIC DRUG INTERACTIONS

Pharmacodynamic interactions have not been reported for sucralfate. Its pharmacokinetic interactions with other drugs are presented in Section 2.4.3.4.

2.4.3 PHARMACOKINETICS

Preliminary studies in animals showed sucralfate to be only minimally absorbed following oral administration; thus, extensive pharmacokinetic evaluation of the drug in humans has not been conducted.

2.4.3.1 ABSORPTION

Sucralfate is only minimally absorbed from the GI tract following oral administration; the drug is absorbed as sucrose sulphate. Poor absorption may result from the high polarity and low solubility of the drug in the GI tract.

Studies in animals indicate that only 3-5 % of an oral dose of sucralfate reaches systemic circulation as sucrose sulphate. Following oral administration of multiple doses of the drug (200 mg/kg daily) in animals, sucrose sulphate did not accumulate in plasma.

Since sucralfate exerts its therapeutic effects directly at the site of the ulcer, the duration of action depends on the time that the drug is in contact with this site. The drug's viscous adhesiveness, slow reaction with acid, and high affinity for damaged mucosa contribute to its prolonged action. Binding to the ulcer site has been shown for up to 6 hours following oral administration, and 30 % of the dose is retained within the GI tract for at least 3 hours [1].

2.4.3.2 DISTRIBUTION

Distribution of sucralfate into human body tissues and fluids following systemic absorption has not been determined. The apparent volume of distribution of sucrose sulphate has been determined in animals and is reported to be approximately 20 % of body weight. Following oral administration of sucralfate in animals, the drug is only minimally distributed into tissues. Approximately 95 % of the dose remains in the GI tract, with only small amounts being distributed into liver, kidneys, skeletal muscle, adipose tissue, and skin [1].

It is not known if sucralfate crosses the placenta or is distributed into milk [1].

2.4.3.3 METABOLISM AND EXCRETION

Sucrose sulphate is not metabolized. In animals, more than 90 % of an orally administered dose of sucrose sulphate is excreted unchanged in feces within 48 hours. The small amount (3-5 %) of sucralfate that is absorbed as sucrose sulphate is excreted unchanged in urine within 48 hours [1].

Following IV administration of sucrose sulphate, plasma concentrations decline rapidly and show first-order elimination. In animals, the elimination half-life of sucrose sulphate ranges from 6-20 hours.

Sucrose sulphate is formed in the GI tract following reaction of sucralfate with hydrochloric acid [1].

2.4.3.4 PHARMACOKINETIC DRUG INTERACTIONS

As sucralfate adsorbs bile salts in animals and decreases pepsin activity in humans its ability to influence the absorption of concomitantly administered drugs has been studied.

In dogs, concomitant administration of sucralfate and phenytoin decreased the relative bioavailability of phenytoin to 62 %, but bioavailability was not affected when the drugs were given 2 hours apart. Sucralfate did not affect the absorption of commercially available digoxin, quinidine, propranolol or aminophylline when administered concomitantly, or of tetracycline given 2 hours after sucralfate [20]. Minor changes in the proportion of the dose of digoxin eliminated occurred in healthy subjects given sucralfate simultaneously. These changes were minimised by administering the drugs 2 hours apart [20].

A possible clinically important interaction between sucralfate and warfarin has been reported in 1 patient receiving stable dosages of warfarin (5 mg alternating with 7.5 mg daily) and an unstated dose of sucralfate. After temporary discontinuation of warfarin because of upper gastrointestinal haemorrhage, the drug was restarted at the previous dosage and sucralfate added to the therapeutic regimen. During a week of sucralfate administration, plasma warfarin concentrations were 0.5 to 0.6 mg/L compared with 1.5 to 1.6 mg/L over a 2-month period prior to sucralfate therapy. Over a 9-day period after sucralfate withdrawal, plasma warfarin concentration increased to 1.6 mg/L and prothrombin time subsequently increased to pre-sucralfate levels [21]. Thus, caution is advisable when sucralfate and warfarin are administered concomitantly, and particularly after sucralfate withdrawal if warfarin dosage has been adjusted to maintain prothrombin times.

2.4.3.5 OTHER PHARMACOKINETIC STUDIES

Aluminium absorption during sucralfate therapy is comparable to that during treatment with aluminium hydroxide [22-24]. The theoretical aluminium content of sucralfate (MW 2,385) ranges from 18.2 to 20.7 % by weight in different batches, and a dose of 1 g four times daily provides 728 to 828 mg of aluminium for absorption. Although over 98 % of this amount is eliminated in faeces, urinary aluminium excretion rises 10-fold during sucralfate administration in subjects with normal renal function [24].

2.4.4 TOXICOLOGY

2.4.4.1 SINGLE-DOSE TOXICITY

The acute toxicity data for sucralfate are presented in Table VIII below:

Table VIII Acute toxicity data for sucralfate [25, 26]

Organism	Test Type	Route	Dose	Effect
Infant	TDLo	Oral	1276 mg/kg/3D-	Cardiac: pulse rate
Rat	LD_{50}	Oral	>12 gm/kg	-
Rat	LD_{50}	Intraperitoneal	>4 gm/kg	-
Rat	LD_{50}	Subcutaneous	>4 gm/kg	-
Mouse	LD_{50}	Oral	>8 gm/kg	-
Mouse	LD_{50}	Intraperitoneal	>8 gm/kg	-
Mouse	LD_{50}	Subcutaneous	>8 gm/kg	-

A study was conducted to determine the effects of aspirated sucralfate in rats. To investigate this, large volume aspiration (2 ml/kg) was simulated in freshly tracheostomized rats (n=6, all experimental groups) using normal saline, particulate antacid, and sucralfate adjusted to pH 3.6 and 5.0. Four hours after aspiration, the rats were killed, and their lungs were formalin fixed. Significant increases in lung inflammation were seen by light microscopy in all experimental groups at pH 3.6. Antacid aspirated at pH 5.0 induced significant increases in airway as well as parenchymal inflammation. At pH 3.6, the antacid aspiration led to significant increases in lung oedema and haemorrhage. Sucralfate aspiration produced significant increases in pulmonary haemorrhage at pH 5.0. The microscopic findings were consistent with the acute pulmonary histopathologic changes known to occur after large-volume aspiration of particulate materials, including antacids. Additionally, it was shown that large-volume aspiration of sucralfate produced significant acute pneumonitis, including pulmonary haemorrhage [27].

No serious toxicity was seen in healthy adults following oral administration of a single 12-g dose of sucralfate. Acute oral toxicity studies in animals using sucralfate doses up to 12 g/kg could not establish a lethal dose. Aluminum toxicity occurred in at least one patient with end-stage renal disease who was receiving sucralfate; it was suspected that the toxicity resulted from systemic absorption of aluminum released during dissociation of the drug in the GI tract [28].

2.4.4.2 REPEAT-DOSE TOXICITY

No toxicity reported in animals after the short-term administration of maximum oral doses [1].

2.4.4.3 GENOTOXICITY

Genotoxicity studies have not been conducted for sucralfate.

2.4.4.4 CARCINOGENICITY

Mutagenicity studies have not been conducted with sucralfate to date. No evidence of carcinogenesis was seen in animals receiving oral sucralfate dosages up to 1 g/kg daily (12 times the usual human dosage) for 24 months [1]. The following data for sucralfate have been reported in the review of [redacted] 29]:

Table IX Carcinogenic effects of sucralfate [29]

Test system	Results (without exogenous metabolic system)	Dose
Long-term carcinogenesis assay, mice	-(×0.7)	1000 mg/kg/day
Long-term carcinogenesis assay, rats	- (×1.4)	1000 mg/kg/day

2.4.4.5 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Administration of 50 times the human dose to mice, rats, and rabbits revealed no teratogenic, fetotoxic, reproductive, or fertility effects [1, 30].

2.4.4.5.1 Fertility

Sucralfate has not been reported to impair male or female fertility [31, 32]. No data were found in the public literature.

2.4.4.5.2 Pregnancy

Sucralfate has been listed as Class B substance by the FDA, i.e., no teratogenicity in animals, suggested as acceptable for use in humans due to minimal systemic absorption [30]. sucralfate 1 g (3 times daily) has been compared with lifestyle modifications (controls) for the treatment of heartburn of pregnancy. It has been found that the sucralfate group had a greater number of patients with complete remission of symptoms (heartburn and regurgitation) when compared to controls (90 vs 43 % and 83 vs 27 %, respectively) [30].

2.4.4.5.3 Lactation

It is not known whether sucralfate is excreted in human milk. However, given that little if any is absorbed, transfer would be expected to be minimal [30].

2.4.4.5.4 Studies in Juvenile Animals

Toxicity studies in juvenile animals have not been performed with sucralfate.

2.4.4.6 LOCAL TOLERANCE

Oral tolerance is a systemic hypo-responsiveness of the organism to the fed protein when the organism is fed with protein, then immunized with the protein [33]. Oral tolerance represents the effects of exogenous antigens on the peripheral immune system via the gut. It is a form that antigen drives the development of peripheral immune tolerance [34]. Generally, low doses of orally administered antigens favor active suppression, whereas higher doses favor clonal allergy.

2.4.4.7 OTHER TOXICITY STUDIES

2.4.4.7.1 Antigenicity

Antigenicity has not been reported for sucralfate.

2.4.4.7.2 Immunotoxicity

The regulatory cells mediate the active suppression by the secretion of suppressive cytokines. TGF-β and IL-4 are the dominate cytokines in the suppressive cytokines, and can induce the oral tolerance [34]. In recent years few studies have reported the effects of oral Al exposure on the IL-4. The IL-4 concentration or expression in plasma became significantly higher than that in control group when the healthy humans were injected 10 ml of antacid (Al hydroxide, 59 mg Al/ml) for 6 weeks [35]. Oral Al exposure was adopted in this experiment, and the results showed that Al increased IL-4 level. It indicates that Al has effects on the oral tolerance. When the BALB/c mice were immunized with codfish extract plus sucralfate from the parenteral route, and control mice were immunized with Al hydroxide (Th2 adjuvant) or monophosphoryl lipid A (MPL) (Th1 adjuvant), significantly elevated IL-4 level was observed in Al-treated mice and sucralfate-treated mice compared with the control group [36]. So, Al can increase level of the IL-4.

Male Wistar rats were orally exposed to 0, 64.18, 128.36 and 256.72 mg/kg body weight aluminum trichloride ($AlCl_3$) in drinking water for 120 days, and CIC level was increased, and the immune function of erythrocytes was inhibited [37]. The function of erythrocytes is to remove the CIC from the circulation blood [38]. So, CIC will not be removed by erythrocytes. Complement can also remove CIC [37], but the complement was also reduced by Al exposure [39]. So, CIC was not removed completely and would deposit in the vascular sites. Autoimmune circulating complex diseases were induced by the deposition of CIC [40]. Therefore, the autoimmune diseases, such as autoimmune circulating complex diseases, would be induced by Al exposure.

The effects of Al on $CD4^+$ T lymphocyte are not clear. Al lactate decreased proportion of $CD4^+$ T lymphocyte in mice, while 200 mg/kg Al lactate per day was added in the diet of mice from conception to 6 months of age [41]. [redacted] showed that the proportion of $CD4^+$ T lymphocyte in peripheral blood decreased in workers which exposed Al for mean 2.35 year and mean 16.5 year and the mean concentrations of Al and Fluorine (F) in the air of Al factory are 5.14 mg/m^3 and 1.315 mg/m^3, respectively. As the present of F in this experiment, it is hard to explain if F decreased proportion of the $CD4^+$ T lymphocyte in the Al factory worker. Later [redacted] reported that the proportion of $CD4^+$ T lymphocyte decreased in Al-treated rats [42]. It avoided the effects of F on the proportion of $CD4^+$ T lymphocyte and found that Al decreased the proportion of $CD4^+$ T lymphocyte. In these results Al form, animal model, exposure time and exposure method were different. The exposure time was from 120 days to 16.5 year. And the exposure Al dose was from 0 to 256.72 mg/kg. The experiment conditions were different, but they got same results. It indicates that long time Al exposure will decrease proportion of $CD4^+$ T lymphocyte. On the contrast, [redacted] showed that the proportion of $CD4^+$ T lymphocyte did not change compared with the control group [35].

2.4.4.7.3 Mechanistic Studies

Mechanistic studies on the toxicity of sucralfate have not been published.

2.4.4.7.4 Dependence

Dependence has not been reported for sucralfate.

2.4.4.7.5 Studies on Metabolites

Metabolites of sucralfate have not been identified. Pharmacokinetic studies in animals have demonstrated that there is very little (3-5 %) absorption of orally administered sucralfate from the gastrointestinal tract. These studies utilized ^{14}C-labelled sucralfate. Only small amounts of radioactivity were found in the blood, expired carbon dioxide, and urine of the experimental animals; almost all (90 % or more) of the radioactivity was recovered in the faeces [43].

2.4.4.7.6 Studies on Impurities

The specifications of sucralfate impurities are presented in the following table:

Table X Impurities of sucralfate

[redacted]

Justification of Impurity A (Sucrose heptasulfate-all isomers)

The release and shelf-life specification limit for Impurity A (Sucrose heptasulfate-all isomers) is in accordance with the Ph. Eur. monograph for Sucralfate.

Justification of any other impurity

The limit set for any other impurity is based on the ICH guideline Q3B (R2) "Impurities in new drug products", considering the maximum recommended daily dose of above 2 g of Sucralfate. Thus, a limit of [redacted] is deemed justifiable, as an identification threshold.

Justification of total impurities

The limit set for total impurities is in accordance with batch release and stability data received for the registration batches placed in stability studies. Thus, it is considered fully justifiable.

Given the limited available stability data and based on the ICH Guideline Q6A on Specifications, where it is stated that "at the time of filing it is unlikely that sufficient data will be available to assess process consistency. Therefore, it is considered inappropriate to establish acceptance criteria which tightly encompass the batch data at the time of filing.", it is important that specifications are not set too tightly resulting in unnecessary rejection of batches.

2.4.4.7.7 Excipients

The product under assessment contains the excipients listed in Table XI below.

Table XI Qualitative and quantitative composition of sucralfate 1 g/5 ml oral suspension

Component	Function	[redacted]
Sucralfate	Active ingredient	
Glycerol	Humectant	
Sodium dihydrogen phosphate dihydrate	Buffering agent	
Sodium methyl parahydroxybenzoate	Preservative	

Component	Function	[redacted]
Xanthan gum	Thickener	
Saccharin sodium	Sweetener	
Aniseed	Flavour	
Caramel	Flavour	
Water, purified	Solvent	

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

A brief discussion on the safety of each excipient used follows:

2.4.4.7.7.1 Glycerol

Glycerin, also known as glycerol, is used as an antimicrobial preservative, cosolvent and sweetening agent [44].

Glycerol occurs naturally in animal and vegetable fats and oils that are consumed as part of a normal diet. Glycerol is readily absorbed from the intestine and is either metabolized to carbon dioxide and glycogen or used in the synthesis of body fats. Glycerol is used in a wide variety of pharmaceutical formulations including oral, ophthalmic, parenteral, and topical preparations. Adverse effects are mainly due to the dehydrating properties of glycerol [45]. Oral doses are demulcent and mildly laxative in action. Large doses may produce headache, thirst, nausea, and hyperglycaemia. The therapeutic parenteral administration of very large glycerol doses, 70-80 g over 30-60 minutes in adults to reduce cranial pressure, may induce haemolysis, haemoglobinuria, and renal failure [46]. Slower administration has no deleterious effects [47]. Glycerol may also be used orally in doses of 1.0-1.5 g/kg bodyweight to reduce intraocular pressure. When used as an excipient or food additive, glycerol is not usually associated with any adverse effects and is generally regarded as a non-toxic and non-irritant material.

Reported toxicity data [48]:

- LD_{50} (Guinea pig, Oral): 7.75 g/kg
- LD_{50} (Mouse, IP): 8.70 g/kg
- LD_{50} (Mouse, IV): 4.25 g/kg
- LD_{50} (Mouse, Oral): 4.1 g/kg
- LD_{50} (Mouse, SC): 0.09 g/kg
- LD_{50} (Rabbit, IV): 0.05 g/kg
- LD_{50} (Rabbit, Oral): 27 g/kg
- LD_{50} (Rat, IP): 4.42 g/kg
- LD_{50} (Rat, Oral): 5.57 g/kg
- LD_{50} (Rat, Oral): 12.6 g/kg
- LD_{50} (Rat, SC): 0.1 g/kg

Glycerol is of very low acute toxicity to mammals. The range of acute oral LD_{50} values derived from studies in experimental animals is between >4,000 and < 38,000 mg/kg, with the majority of values being between 23,000 and 38,000 mg/kg. For acute dermal toxicity a single LD_{50} of >18,700 mg/kg for rabbits is available. No information is available on the acute toxicity of inhaled glycerol. Glycerol is more toxic when administered intravenously, intraperitoneally or subcutaneously [49].

Mild osmotic diuresis occurs after oral glycerol doses of 1.0-1.3 g glycerol/kg bw [50]. Following oral administration of 0.75-1.5 g/kg bw in a 50 %-75 % solution, a relatively rapid increase in serum osmolality occurs, leading to a reduction of intraocular and intracranial pressure. This dose level is used as treatment for acute glaucoma in children as well as adults. The effect on intraocular pressure may last for 4 to 10 hours. Thirty minutes after ingestion of glycerol at a dose of 1 g/kg bw the intracranial pressure was 4 times lower than before glycerol administration, and normalized after 4 hours [51].

The usual dose is 2 grams twice daily to be taken on rising and at bedtime, or 1 gram 4 times a day to be taken 1 hour before meals and at bedtime. Maximum daily dose: 8 grams. This corresponds to 4 g of sucralfate administered as singled dose (or 20 ml of the product under assessment).

The concentration of glycerol on the product under evaluation is [redacted] the maximum single administered dose of glycerol is [redacted] Both the EMA safety limit of 10 g/dose or the EFSA limit for the therapeutic dose of glycerol [redacted] patients above 14 years of age (>40 kg) are not exceeded.

2.4.4.7.7.2 Sodium dihydrogen phosphate dihydrate

Monobasic sodium phosphate is widely used as an excipient in parenteral, oral, and topical pharmaceutical formulations [52].

Phosphate occurs extensively in the body and is involved in many physiological processes since it is the principal anion of intracellular fluid. Most foods contain adequate amounts of phosphate, making hypophosphatemia [53] virtually unknown except in certain disease states [54] or in patients receiving total parenteral nutrition. Treatment is usually by the oral administration of up to 100 mmol of phosphate daily.

Approximately two-thirds of ingested phosphate is absorbed from the gastrointestinal tract, virtually all of it being excreted in the urine, and the remainder is excreted in the feces.

Excessive administration of phosphate, particularly intravenously, rectally, or in patients with renal failure, can cause hyperphosphatemia that may lead to hypocalcaemia or other severe electrolyte imbalances [55-57]. Adverse effects occur less frequently following oral consumption; although, phosphates act as mild saline laxatives when administered orally or rectally (2-4 g of monobasic sodium phosphate in an aqueous solution is used as a laxative). Consequently, gastrointestinal disturbances including diarrhoea, nausea, and vomiting may occur following the use of monobasic sodium phosphate as an excipient in oral formulations. However, the level of monobasic sodium phosphate used as an excipient in a pharmaceutical formulation is not usually associated with adverse effects.

Reported Toxicity data for Monobasic Sodium Phosphate [58]:

- LD_{50} (Rat, IM): 250 mg/kg
- LD_{50} (Rat, Oral): 8,290 mg/kg

2.4.4.7.7.3 Sodium methyl parahydroxybenzoate

Sodium methyl hydroxybenzoate (methylparaben) and other parabens are widely used as antimicrobial preservatives in cosmetics and oral and topical pharmaceutical formulations [59]. Although parabens have also been used as preservatives in injections and ophthalmic preparations, they are now generally regarded as being unsuitable for these types of formulations owing to the

irritant potential of the parabens. These experiences may depend on immune responses to enzymatically formed metabolites of the parabens in the skin.

Parabens are non-mutagenic, non-teratogenic, and non-carcinogenic. Sensitization to the parabens is rare, and these compounds do not exhibit significant levels of photocontact sensitization or phototoxicity. Hypersensitivity reactions to parabens, generally of the delayed type and appearing as contact dermatitis, have been reported. However, given the widespread use of parabens as preservatives, such reactions are relatively uncommon; the classification of parabens in some sources as high-rate sensitizers may be overstated. Immediate hypersensitivity reactions following injection of preparations containing parabens have also been reported [60-62]. Delayed-contact dermatitis occurs more frequently when parabens are used topically, but has also been reported to occur after oral administration [63, 64]. Unexpectedly, preparations containing parabens may be used by patients who have reacted previously with contact dermatitis provided they are applied to another, unaffected, site. This has been termed the paraben paradox [65]. Concern has been expressed over the use of methylparaben in infant parenteral products because bilirubin binding may be affected, which is potentially hazardous in hyperbilirubinemic neonates [66]. The WHO has set an estimated total acceptable daily intake for methyl-, ethyl-, and propylparabens at up to 10 mg/kg bodyweight [67].

Given the maximum daily intake of sucralfate (8 grams of sucralfate or 40 ml of suspension) and the concentration of paraben on the product under evaluation [redacted], it is evident that the WHO ADI of 10 mg/kg bodyweight is not exceeded for patients above the 14 years of age, i.e., patients with body weight > 40 kg.

Reported toxicity data [68]

- LD_{50} (Dog, Oral): 3.0 g/kg
- LD_{50} (Mouse, IP): 0.96 g/kg
- LD_{50} (Mouse, SC): 1.20 g/kg

A warning for the potential of allergic reactions (possibly delayed), has been added in relevant section of the SmPC of the product under assessment, in accordance with the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668, Rev. 4).

2.4.4.7.7.4 Xanthan gum

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent. It is non-toxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range [69].

Xanthan gum has been used as a suspending agent for conventional, dry and sustained-release suspensions. Although primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablets.

The estimated acceptable daily intake for xanthan gum has been set by the WHO at up to 10 mg/kg body-weight [70].

No eye or skin irritation has been observed in rabbits and no skin allergy has been observed in guinea pigs following skin exposure. No adverse effects were observed in long-term feeding studies with rats

(up to 1000 mg/kg/day) and dogs (up to 1000 mg/kg/day). No adverse effects were observed in a three-generation reproduction study with rats (up to 500 mg/kg/day) [69].

Reported toxicity data [69-71]:

- LD_{50} (Dog, Oral): > 20 g/kg
- LD_{50} (Rat, Oral): > 45 g/kg
- LD_{50} (Mouse, Oral): > 1 g/kg
- LD_{50} (Mouse, IP): > 50 mg/kg
- LD_{50} (Mouse, IV): 100-250 mg/kg

2.4.4.7.7.5 Saccharin sodium

Saccharin sodium is an intense sweetening agent used in beverages, food products, table-top sweeteners, and pharmaceutical formulations such as tablets, powders, medicated confectionery, gels, suspensions, liquids, and mouthwashes [72, 73];. It is also used in vitamin preparations.

Saccharin sodium is considerably more soluble in water than saccharin and is more frequently used in pharmaceutical formulations. Its sweetening power is approximately 300-600 times that of sucrose. Saccharin sodium enhances flavour systems and may be used to mask some unpleasant taste characteristics. Injection of saccharin sodium has been used to measure the arm-to-tongue circulation time [72].

There has been considerable controversy concerning the safety of saccharin and saccharin sodium in recent years; however, it is now generally regarded as a safe, intense sweetener. The WHO has set a temporary acceptable daily intake of up to 2.5 mg/kg body-weight for saccharin, including its salts [74]. In the EU, the Scientific Committee for Food (SCF) has set an acceptable daily intake for saccharin and its salts (expressed as saccharin sodium) at up to 5 mg/kg body-weight [75].

Reported toxicity data [76]:

- LD_{50} (Mouse, Oral): 17.5 g/kg
- LD_{50} (Rat, IP): 7.1 g/kg
- LD_{50} (Rat, oral): 14.2 g/kg

The maximum daily administered volume of the product under assessment is 40 ml, corresponding to 8 gr of sucralfate and [redacted] of saccharin sodium. Given that the product under assessment is indicated for patients above the 14 years of age (i.e., >40 kg), it is evident that both WHO and EUSCF acceptable daily intakes of saccharin and its salts are not exceeded.

2.4.4.7.7.6 Aniseed flavour

The product under assessment contains aniseed flavour at the concentration of [redacted]. Aniseed flavour contains propylene glycol [redacted] Given the maximum administered dose of 8 gr of sucralfate (at 40 ml of the proposed oral suspension), the maximum daily administered amount of propylene glycol is [redacted] Considering also the proposed product is recommended only for adults and children aged >14 years (i.e., >50 kg), the EMA threshold of 50 mg/kg/day is not exceeded and therefore no safety concerns are expected.

2.4.4.7.7.7 *Caramel flavour*

The product under assessment contains caramel flavour at the concentration of [redacted]. Caramel flavour contains propylene glycol [redacted] Given the maximum administered dose of 8 gr of sucralfate (at 40 ml of the proposed oral suspension), the maximum daily administered amount of propylene glycol is [redacted] Considering also the proposed product is recommended only for adults and children aged >14 years (i.e., >50 kg), the EMA threshold of 50 mg/kg/day is not exceeded and therefore no safety concerns are expected.

2.4.5 INTEGRATED OVERVIEW AND CONCLUSIONS

Peptic ulcer disease is known as one of the leading causes of death in the world, caused by an imbalance of invasive factors against gastric protective factors.

Sucralfate exerts a generalised cytoprotective effect by preventing gastrointestinal mucosal injury. Studies in humans and animal models show that sucralfate forms an ulcer adherent complex with the proteinaceous exudate of the ulcer site. This property enables sucralfate to form a protective barrier over the ulcer lesion giving sustained protection against the penetration and action of gastric acid, pepsin and bile. Sucralfate also directly inhibits pepsin activity and absorbs bile salts.

Sucralfate is only minimally absorbed from the gastro-intestinal tract. The small amounts that are absorbed are excreted primarily in the urine.

There was no evidence of carcinogenesis in animal studies. No toxicity reported in animals after the short-term administration of maximum oral doses, and no tumorigenicity was observed after 12 times the human dose was given to animal for 24 months. Likewise, administration of 50 times the human dose to mice, rats, and rabbits revealed no teratogenic, fetotoxic, reproductive, or fertility effects.

The excipients employed in the proposed formulation commonly used in the pharmaceutical industry and no safety issues are expected.

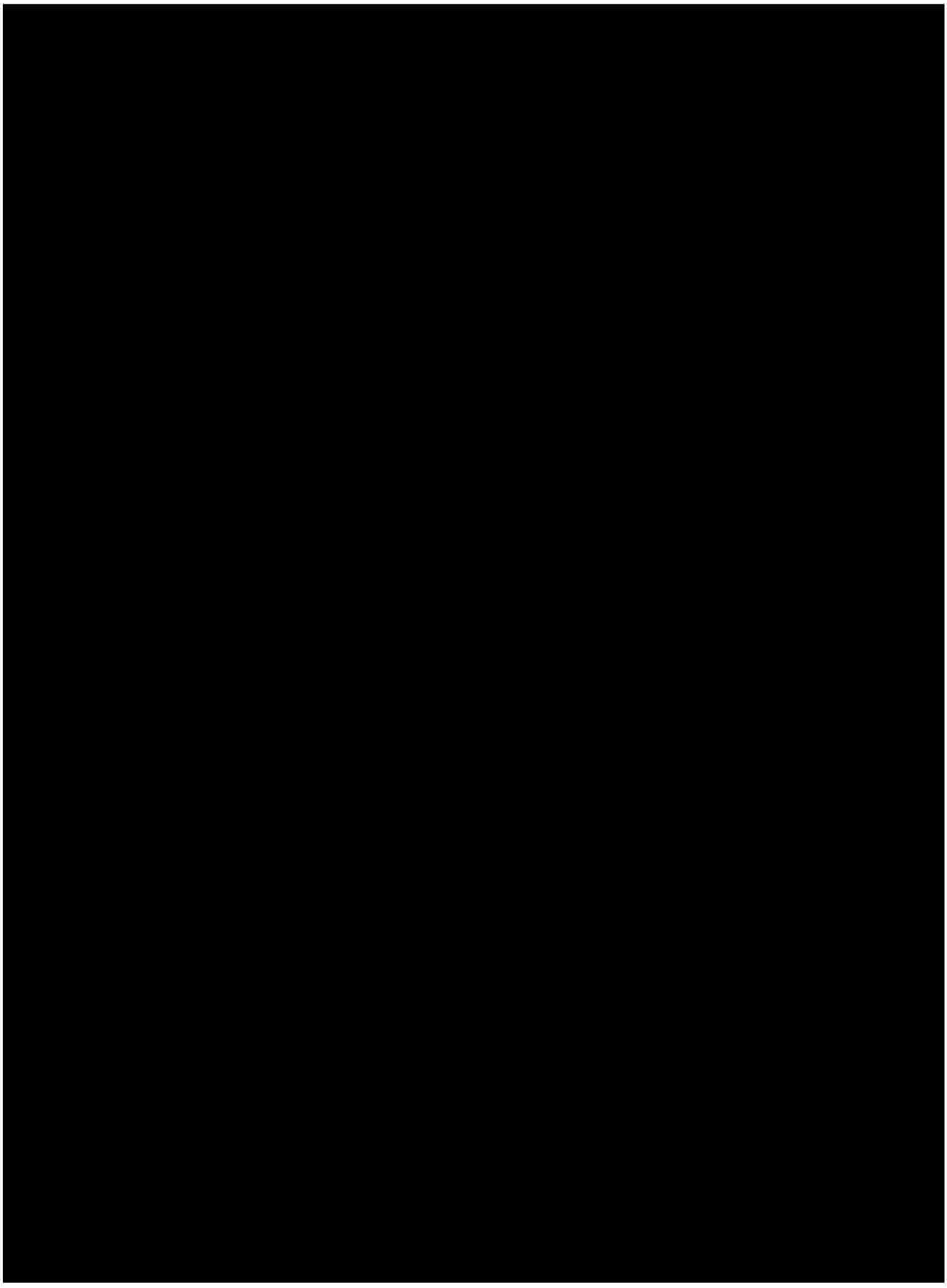
All the available preclinical information suggests that sucralfate has a safety pharmacology and toxicity profile that will not preclude its clinical use according to the restrictions addressed in the proposed SmPC.

The characteristics of sucralfate are adequately reflected in the proposed SmPC and the indications and precautions for the use of this medicinal product are justified by its pharmacological properties.

The benefit-risk profile of sucralfate is considered to be favourable, provided that the product is used according to the SmPC. Overall, it can be stated that the investigations performed on sucralfate cover all aspects of safety assessment required and can therefore demonstrate an acceptable level of safety for sucralfate under the conditions stipulated in the SmPC and marketing authorisation should be granted for the proposed product.

2.4.6 LIST OF LITERATURE REFERENCES

2.4 Nonclinical overview



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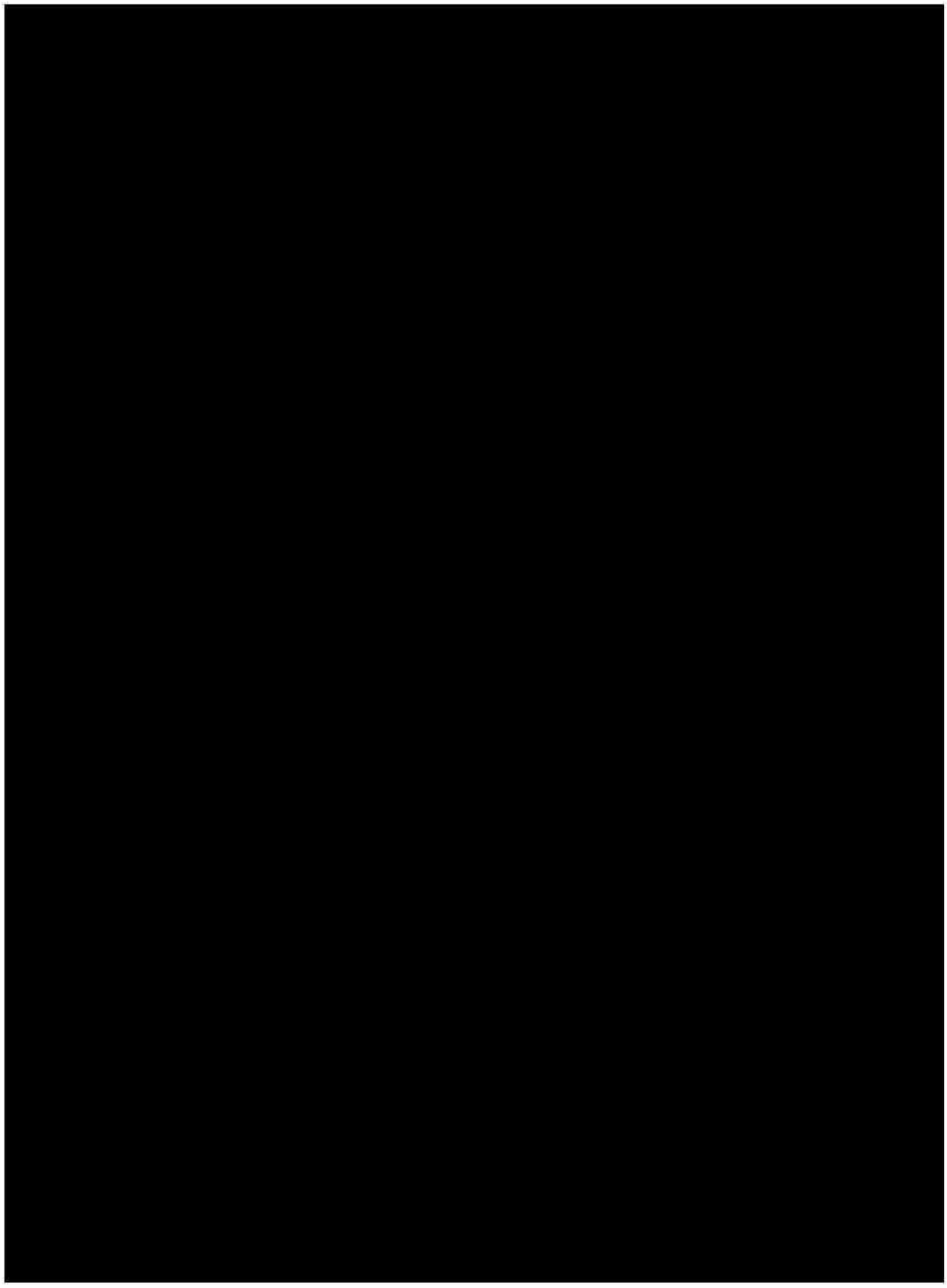

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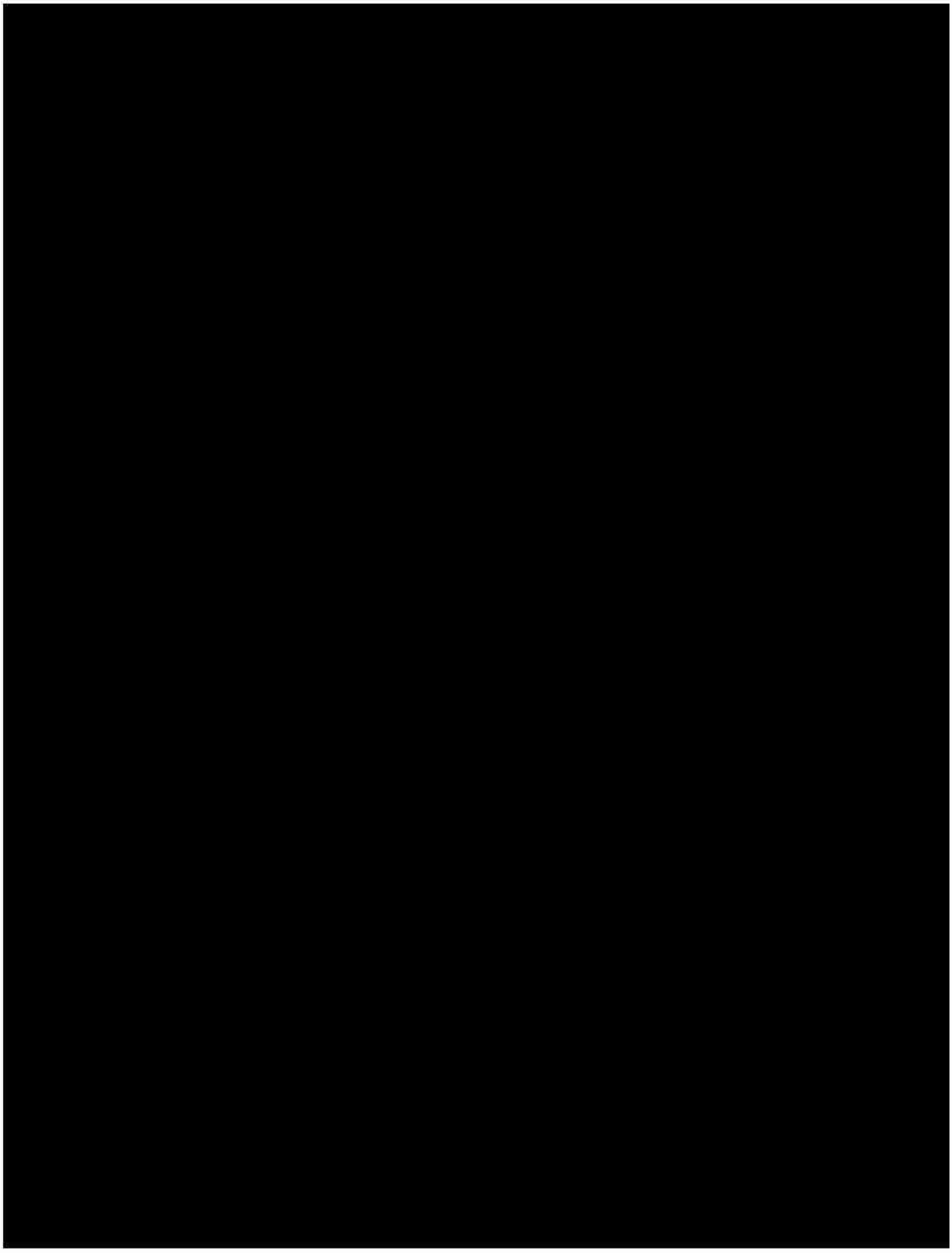

2.4 Nonclinical overview