

2.5 Clinical Overview

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LIST OF ABBREVIATIONS

AIFA	Agenzia Italiana del Farmaco
AN	Acid Neutralizing
API	Active Pharmaceutical Ingredient
BID	Twice a day
BSA	Bovine Serum Albumin
CBS	Colloidal Bismuth Subcitrate
CI	Confidence Interval
CP	Comparator Product
EGF	Epidermal Growth Factor
EU	European Union
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
GCP	Good Clinical Practice
GI	Gastrointestinal
GMA	Global Marketing Authorisation
GU	Gastric Ulcer
HSA	Human Serum Albumin
ICU	Intensive Care Unit
IV	Intravenous
MAH	Marketing Authorization Holder
MHRA	Medicines and Healthcare products Regulatory Agency
MW	Molecular Weight
NSAID	Nonsteroidal Anti-Inflammatory Drug
PCS	Parietal Cell Sensitivity
PD	Pharmacodynamics
PK	Pharmacokinetics
PN	Nosocomial Pneumonia
PPIs	Proton Pump Inhibitors
q.d.s.	Once a day
q.i.d.	Four times a day
RMP	Reference Medicinal Product
SmPC	Summary of Product Characteristics
SOS	Sucrose Octasulphate
SUC	Stress Ulcer Prophylaxis

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2.5.1 PRODUCT DEVELOPMENT RATIONALE

This Clinical Overview examines the current state of scientific knowledge available on the general clinical 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.

2.5.1.1 CHEMICAL CHARACTERIZATION

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·mol ⁻¹	
Identifiers		
CAS number	54182-58-0	
ATC code	A02BX02	
ATC Groups	1 st Level	A: Alimentary tract and metabolism
	2 nd Level	A02: Drugs for acid related disorders
	3 rd Level	A02B: Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)
	4 th 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	

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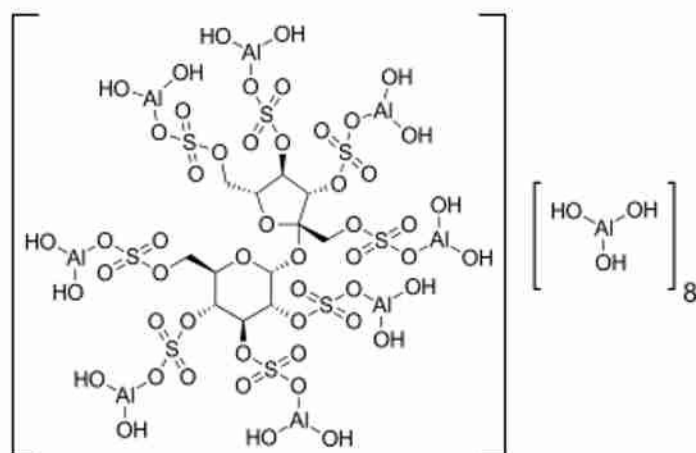


Figure 1: Chemical structure of sucralfate

2.5.1.2 PHARMACOLOGICAL PROPERTIES

Sucralfate is a sulphated disaccharide, basic aluminium sucrose sulphate complex. Its development is the result of a lot of studies on sulphated polysaccharides, well-known for their anti-peptic activities and also, for their anticoagulant activities. Sucralfate is free from toxicity, including anticoagulant activity like all the disaccharides and is an antiulcer agent better than other drugs of its chemical family. Sucralfate is characterized by the following properties: When exposed to gastric acid, it turns into a viscous and adhesive substance which binds selectively and durably to the lesions of gastric and duodenal mucosa. The affinity of sucralfate for defective mucosa is explained by the formation of electrostatic bindings between the negatively charged sucralfate polyanions and the positively charged proteins exuding from lesions [1].

That following explain the absence of systemic effects and of toxicity:

- Barrier effect to the penetration of acid, pepsin and bile salts.
- Interference with binding of the pepsin with the lesions.
- Adsorption of pepsin and bile salts.
- Protection of normal mucosa weakness of the reaction with acid.
- Possibility of stimulation of synthesis of local prostaglandins.
- Sucralfate is slightly absorbed by the digestive mucosa.

Its pharmacodynamic effects corroborated by good therapeutical results make sucralfate an original antiulcer drug which leads a new way in the treatment of peptic disease [1].

2.5.1.3 INFORMATION ABOUT THE CONDITION

Peptic ulcer disease is known as one of the leading causes of death in the world. This disease is caused by an imbalance of invasive factors against gastric protective factors [2]. This disease occurs when the protective mechanisms of the gastrointestinal mucosa are affected by the destructive effects of stomach acid and pepsin [3]. In other words, stomach acid causes a gap in the mucosa and reaches the subcutaneous layer. These ulcers are usually found in the stomach and duodenum but can also occur in the oesophagus [4]. On the other hand, ulcers may develop in unusual areas, such as the ileum, due

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to Meckel's diverticulum, inlet patch in the proximal oesophagus, or in the jejunum due to excessive acid secretion in Zollinger-Ellison syndrome [4].

One of the main symptoms of this disease is epigastric pain. Other symptoms include indigestion, bloating, premature satiety, nausea, heartburn, and bleeding. The most common symptom of peptic ulcer disease, which is more common in people over 60 years of age, is bleeding and 50 to 170 out of every 100,000 people suffer from this complication. Taking NSAID drugs and *Helicobacter pylori* infections are the most common aetio-pathogenic symptoms of bleeding in the peptic ulcer disease [5, 6].

The prevalence of this disease in the world is reported to be 5-10 % [4]. However, meta-analyses in eastern populations have reported higher prevalence (i.e., 34 % in Iran [7], 21.9 % in Saudi Arabi [8]). The prevalence of peptic ulcer in the world has different and heterogeneous reports [9, 10]. Recently, the prevalence of peptic ulcer in the world (age range of 17-82 years) was obtained as 8.4 % [11].

2.5.1.4 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 () [12, 13].

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, () 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 () 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 [14]. 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.

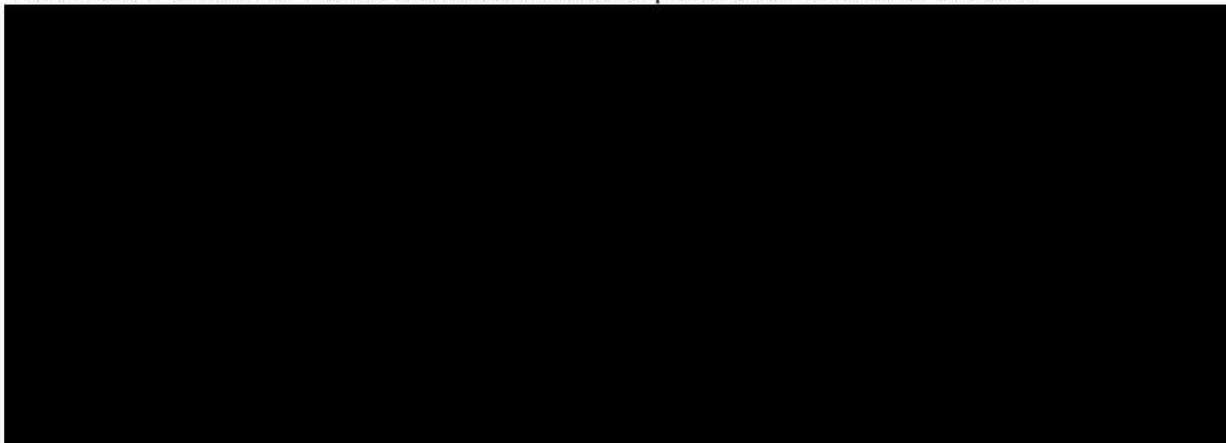
Following its withdrawal from the UK market, the Italian version of Antepsin 1 g/5 ml Oral Suspension has been imported into the UK (PLPI 15814/1328). This product is manufactured by Laboratori Baldacci S.p.A. and repackaged by O.P.D. Laboratories Ltd., the Product Licence holder, under licence from Chugai/Fuji [15, 16].

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

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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) [17], which is the same as the currently available on the UK market through parallel import.

The figure below illustrates the updated bridging rationale linking the test product to published clinical evidence for sucralfate. Two EU-authorized reference products have been considered:



The test product formulation falls within the formulation space defined by the totality of published sucralfate literature, providing additional supportive evidence.

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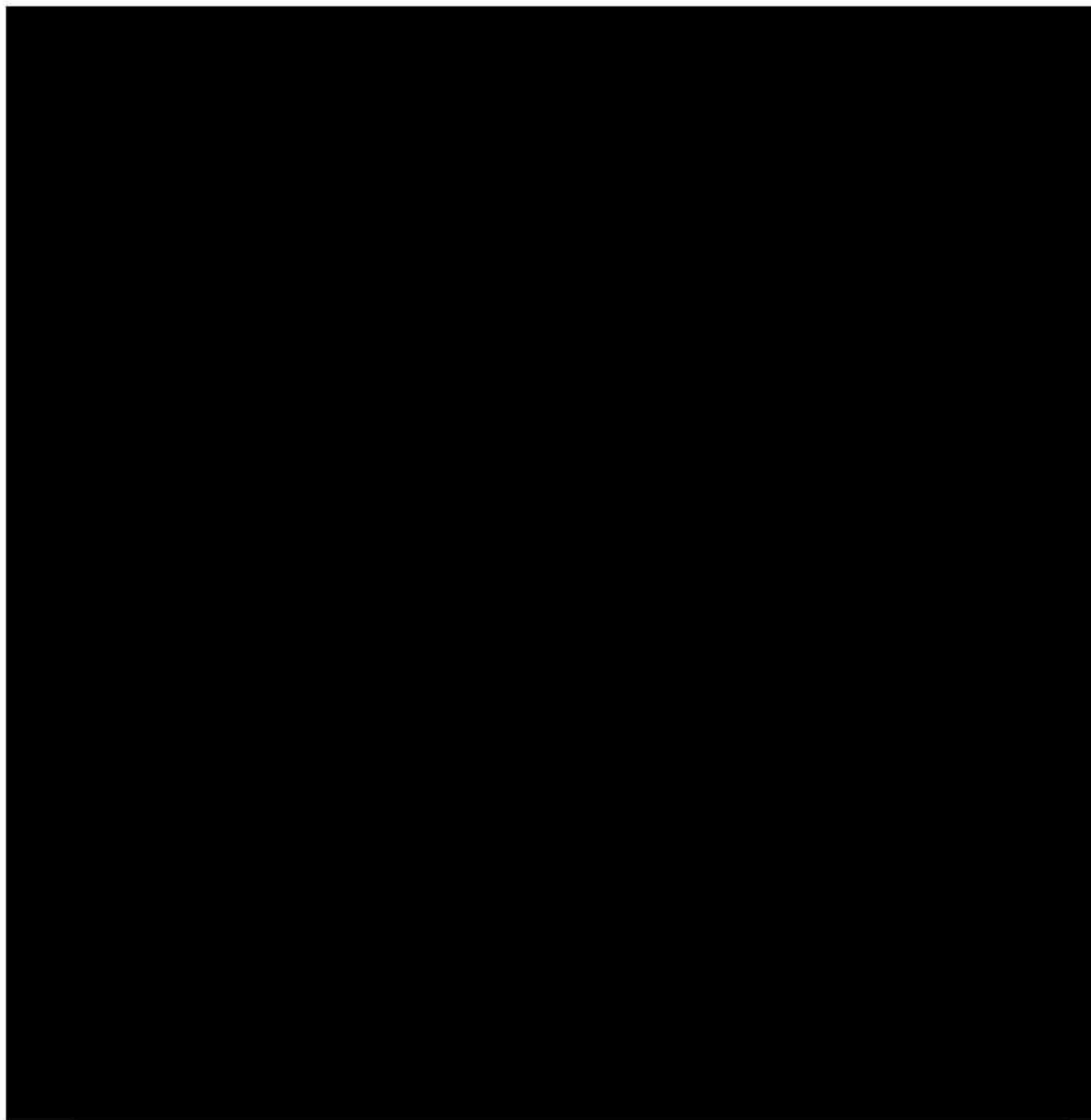


Figure 2 Bridging strategy; Legend: Solid arrows = confirmed relationship; Dashed arrows = presumed relationship.

2.5.1.4.1 Selection of the Italian Comparator Product

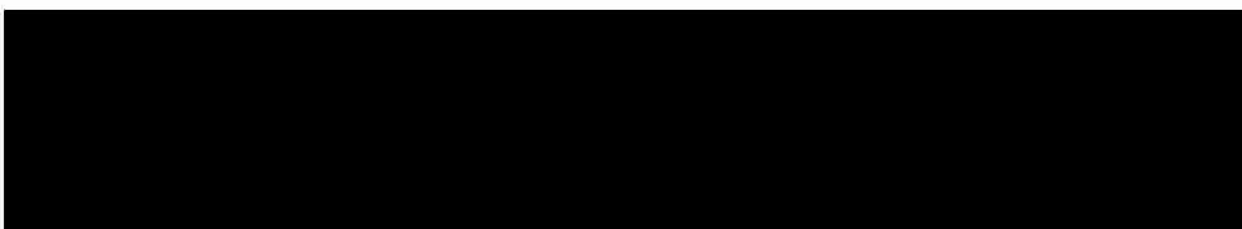
The selection of the Italian comparator product for comparison with the candidate formulation was based on the outcome of the pre-Windsor Framework Scientific Advice meeting with the MHRA. The rationale for this selection includes:

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1. Regulatory precedent: The Italian product represents a full marketing authorization dossier within the EU regulatory framework.
2. Market availability: The product is authorized in Italy and has been subject to parallel import into the UK market, thereby representing a medicinal product that has been accessible to UK patients.
3. Historical UK market presence: The Italian product shares the same tradename (Antepsin) as the previously licensed UK product marketed by Chugai Pharmaceutical, indicating a commercial and potentially regulatory relationship between the two authorizations.

Based on these factors and following MHRA guidance during the pre-Windsor Framework Scientific Advice procedure, the Italian comparator was considered the most appropriate reference product for this application.

2.5.1.4.2 Attempts to Establish Global Marketing Authorization (GMA) Linkage



2.5.1.4.3 Publicly Available Evidence Supporting Product Linkage

In the absence of direct GMA confirmation from the MA holder, the applicant has identified publicly available regulatory and commercial evidence that establishes an indirect connection between the UK and Italian products:

2.5.1.4.3.1 Evidence from Italian Regulatory Authority (2008)

The Italian Gazzetta Ufficiale published a regulatory variation in 2008 documenting the replacement of the active pharmaceutical ingredient (API) manufacturer for sucralfate products marketed in Italy. Specifically:

- Original API manufacturer: Chugai Pharma Manufacturing Co. Ltd, Fujieda plant (Japan)
- New API manufacturer: [REDACTED]

Reference [REDACTED]



2.5.1.4.3.2 Common Tradename and Marketing Authorization Holder History

Both the UK product (withdrawn 2019) and the Italian product (currently authorized) were marketed under the tradename "Antepsin", which was owned by Chugai Pharmaceutical. The use of the same tradename across multiple jurisdictions is typically indicative of:

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- A common Global Marketing Authorization (GMA) strategy
- Shared formulation development and regulatory dossiers
- Coordinated manufacturing and supply arrangements

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.

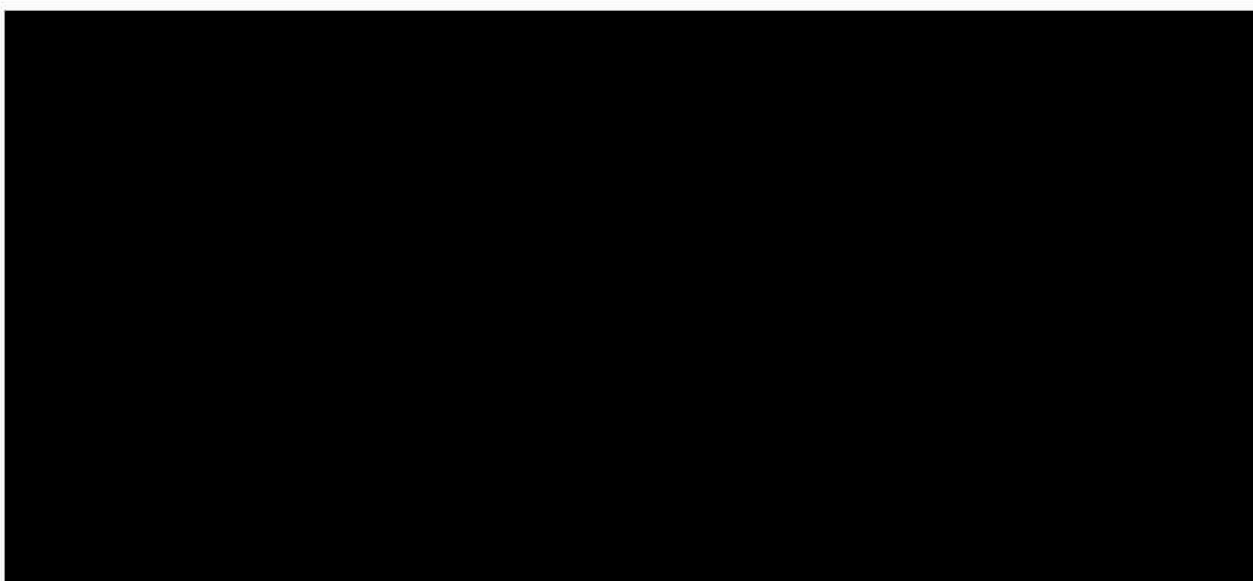
2.5.1.5 CLINICAL DEVELOPMENT PROGRAMME

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 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) [23] 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 present document and in Module 5.3.1.2.

2.5.1.6 SEARCH STRATEGY



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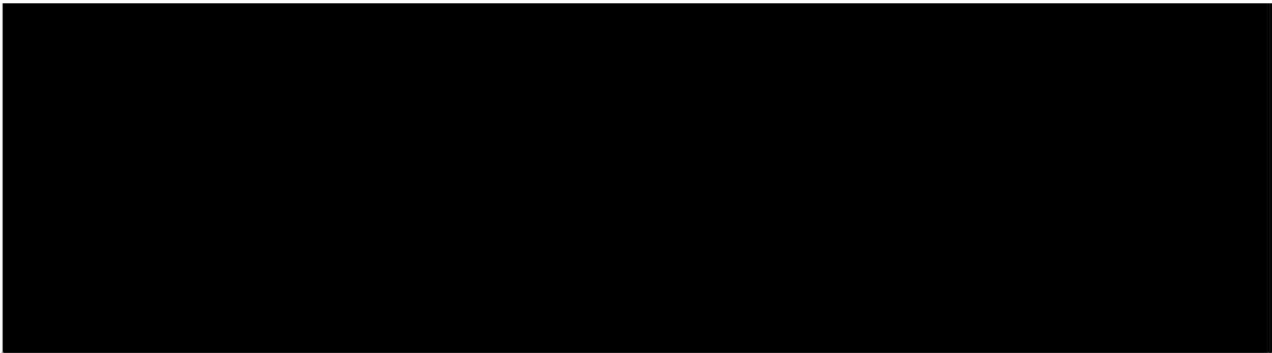


Table II Literature Search Methodology



This Clinical Overview is substantially based on literature reviews collected in searches #4 - #6, i.e. reviews of the scientific literature which focus on the active substance and systematic reviews including the active substance. These citations were single screened for relevancy. Articles cited in the relevant reviews were collected and included in this report, irrespectively of whether they appeared in the search results of the MEDLINE database. Individual sections of this overview were supported by searches #7-#12, mainly to fill in gaps or to update each section with the latest published information.

Unfortunately, the GCP status of the clinical studies has not been declared in all the published clinical papers. However, nearly all the studies were conducted in renowned clinics in developed countries. It

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can consequently be assumed that the GCP rules were used, in principle, even if the latter are not mentioned specifically in the publications.

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

2.5.2.1 BIOEQUIVALENCE STUDY

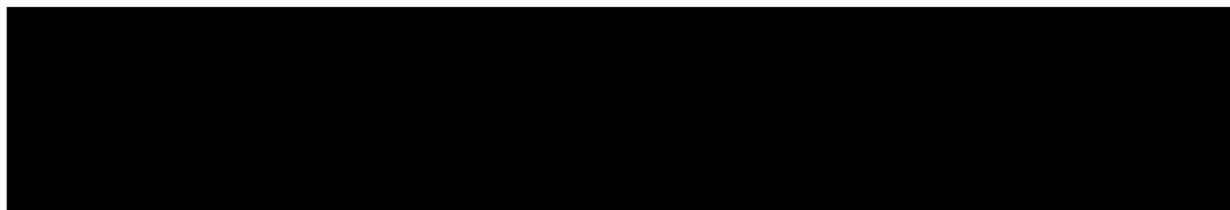
The clinical development programme is based on in vitro studies, as recommended by the draft US FDA guidance for sucralfate suspension. The Applicant intends has compared the product under assessment, Sucralfate 1 g/5 ml oral suspension with the Italian product imported to UK product Antepsin 1 g/5 ml Oral Suspension (15814/1328) through the following in vitro studies (based on US FDA draft guidance on sucralfate suspension [23]).

The below studies are also in accordance with the Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev. 1, Corr.1*) which states that for those products with a mechanism of action based on binding to components of the GI milieu through the whole intestine (e.g. cholestyramine, colestipol, calcium acetate, sevelamer) in vitro studies based on their binding capacity (e.g. in-vitro equilibrium and dynamic binding studies) are considered acceptable surrogates for the assessment of efficacy.

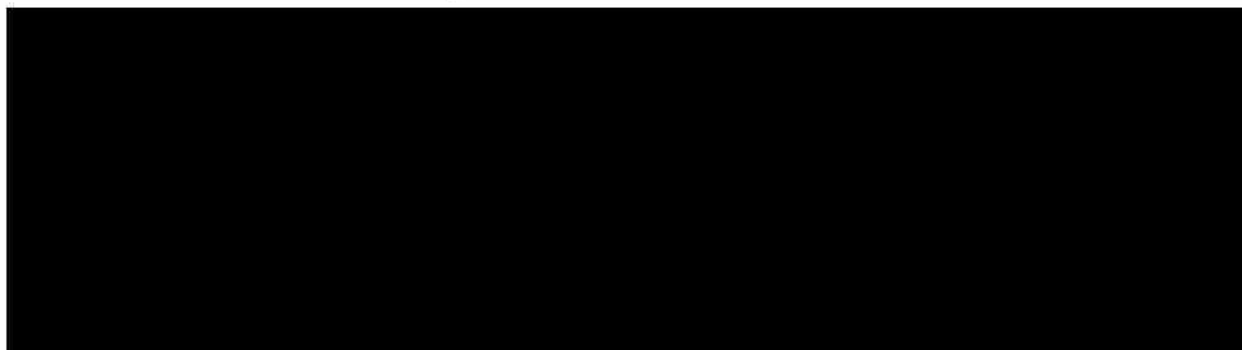
2.5.2.1.1 In vitro equivalence studies with Antepsin 1 g/5 ml Oral Suspension

I. Sameness of Active Pharmaceutical Ingredient

The API sameness of the product under assessment and Antepsin 1 g/5 ml Oral Suspension has been demonstrated through the following characterisations:



The results of the above studies are provided in Module 3.2.P.2.



The results of the above studies are provided in Module 3.2.P.2.

III. Bioassays of the Test and Reference Formulations

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A summary of the in vitro studies results is provided in the following paragraphs. The full study reports are provided in Module 5.3.1.2.

1. In vitro equilibrium binding study with Bovine Serum Albumin (BSA)

The acid pre-treated formulations are used in the equilibrium binding study. Eight different concentrations of BSA were used in the study. Assays were performed under conditions relevant to the in vivo physiological conditions. The equivalence is based on the 90 % CI of Langmuir binding constant k_2 from the equilibrium binding study.

The BSA binding profile of test/reference was compared and the affinity (k_1) and capacity (k_2) constants of the BSA was calculated using linear regression for test and reference products.

The 90 % CI for k_2 was calculated and T/R ratios were calculated for k_2 .

Table III 90% CI for the Langmuir binding constant k_2 (Assessment of bioequivalence)

Parameter	Test	Reference	Ratio T/R	90 % CI	
	Mean			Lower	Upper
k ₂	235.2636	224.5869	104.75	98.61	110.89

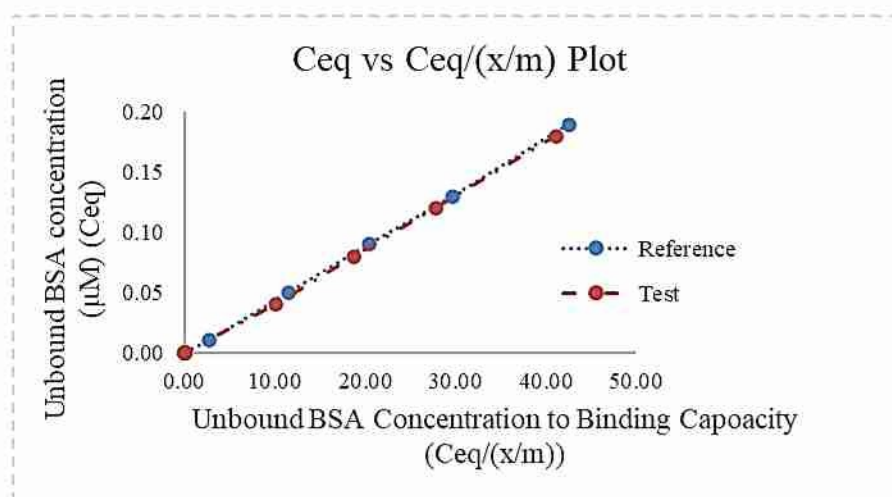


Figure 3 Representation of Langmuir plot for Test & Reference Product

The experimental data indicate that the concentration of BSA bound to test and reference products at the BSA spiking concentration was similar. The increase of BSA binding over the BSA concentration gradient 76.36 μM to 14.85 μM indicates that the maximum binding was achieved.

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The maximum % binding (~100 % BSA binding) was observed at 30.76 μ M to 14.85 μ M - BSA concentration and minimum percentage binding was observed at 76.36 μ M- BSA concentration (maximum spiking concentration).

The 90 % CI of ratio estimated by the Langmuir linear regression for capacity constant (k_2) was found to be within the set limits of the bioequivalence i.e., 80 % to 120 %. Therefore, the test and reference product are bioequivalent in terms of Capacity Constant.

2. In vitro equilibrium binding study with bile salts

The same study design as in In vitro equilibrium binding study with BSA is applied.

The affinity (K_1) and capacity (K_2) constants of the total bile acids (GCA, GCDCA & TDCA) were determined using Langmuir equation for test and reference products. The 90 % CI for K_2 was calculated, and the Test/Reference ratios were calculated for K_1 and K_2 .

Table IV 90 % CI for Test/Reference ratio for K_2 and mean T/R percent ratio for K_2 with linear regression (with acid pretreatment, pH 4.0).

Parameter	With acid pretreatment, pH 4.0			
	Mean Test (T)	Mean Reference (R)	Mean Test/Reference percent ratio (T/R)	90 % CI for Test/Reference ratio (Limit: 80%-120%)
Capacity Constant (K_2)	152.7096	150.8927	152.7096	98.79 - 103.61

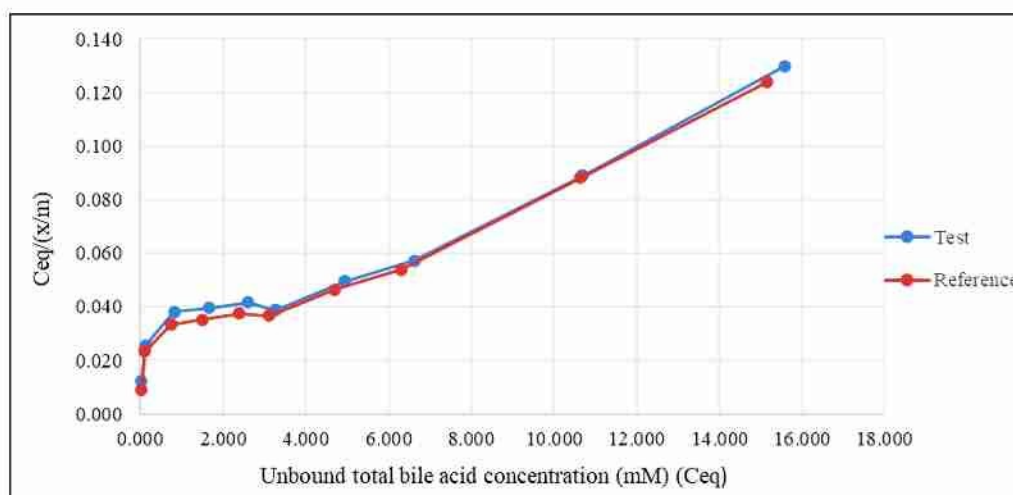


Figure 4 Langmuir plot of Test and Reference product at pH 4.0

Based on experimental data and statistical analysis, it is evident that the test product and reference product are bioequivalent in terms of capacity constant.

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3. *In vitro* kinetic binding study with bile salts

The same study design as in *In vitro* equilibrium binding study with BSA is applied. This study was conducted by incubating the acid pre-treated formulations for at least eight different lengths of time, with two different constant bile salt concentrations. The equivalence is based on the qualitative comparison between the formulations with respect to the % binding of bile salts to sucralfate.

The applicant compared the kinetics of bile salts (GCA, GCDCA & TDCA) binding (for eight different lengths of time, with two different bile acid salts concentrations (0.5 mM and 40.0 mM concentration, selected as per guidance) to Sucralfate in test product (Sucralfate 1 g/5 ml Oral Suspension) with that of the reference product [Antepsin® Sospensione Orale (Oral Suspension) 1 g/5 ml].

The study was conducted with acid pre-treatment by incubating the test and reference products with two bile salts concentration (GCA, GCDCA & TDCA) (0.5 mM and 40.0 mM concentrations selected as per guidance) at a temperature of $37 \pm 0.5^\circ\text{C}$ for eight different lengths of time [i.e., 00.50 (30 min), 01.00, 02.00, 03.00, 04.00, 08.00, 18.00 and 24.00 hours]. The unbound total bile salts concentration in the filtrate [to calculate bile acids (GCA, GCDCA & TDCA) bound to resin] was measured.

The results are summarised below:

- The mean % binding of Bile acids to Test and Reference products was ranging from 74.277 to 97.055 and 74.870 to 96.858 at the 0.5 mM concentration respectively from 00.50 hr to 24.00 hr.
- The mean % binding of Bile acids to Test and Reference products was ranging from 46.060 to 58.870 and 48.323 to 59.513 at the 40 mM concentration respectively from 00.50 hr to 24.00 hr.
- The mean binding capacity (x/m) (mM/g) to Test product and Reference product was ranging from 1.935 to 2.529 and 1.951 to 2.523 at the 0.5 mM concentrations respectively from 00.50 hr to 24.00 hr.
- The mean binding capacity (x/m) (mM/g) to Test product and Reference product was ranging from 89.807 to 114.74 and 94.185 to 115.999 at the 40 mM concentrations respectively from 00.50 hr to 24.00 hr.
- The obtained results indicate that the test product and reference product are similar in terms of kinetic profile.

The maximum binding was achieved in the range of 8.00 hr to 24.00 hrs for both test and reference products at constant bile acids concentration of 0.5 mM and 40 mM.

4. *In vitro* enzyme (pepsin) activity study

The acid pre-treated formulations were used in the enzyme activity study and at least five different concentrations of both formulations were used in the study. Assays were performed under conditions relevant to the *in vivo* physiological conditions. The equivalence is based on the qualitative comparison between the formulations with respect to the % decrease in pepsin activity.

The T/R ratio of % decrease/inhibition of pepsin activity at different sample concentrations of test and reference products is presented in the following table:

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Table V Comparison of T/R ratios of % decrease in pepsin activity

Replicate	Sucralfate concentration				
1	100.60	102.45	102.10	99.04	95.25
2	100.51	102.37	102.15	98.93	96.80
3	102.66	100.30	99.61	101.24	103.22
4	100.32	100.50	99.07	98.40	102.67
5	98.50	102.48	102.49	103.22	109.57
6	98.41	102.36	102.50	102.56	108.69
7	99.94	99.88	98.60	99.00	97.20
8	99.92	99.83	98.55	99.00	97.04
9	99.94	99.85	100.11	100.94	100.16
10	99.90	99.81	100.33	100.84	100.16
11	100.67	100.86	99.74	105.44	104.81
12	100.54	100.84	99.74	105.33	104.59
N	12.00	12.00	12.00	12.00	12.00
Mean	100.16	100.96	100.42	101.16	101.68
SD	1.09	1.13	1.50	2.50	4.71
RSD (%)	1.09	1.12	1.49	2.47	4.63

The assessment of equivalence is based on the % RSD between T/R ratios of inhibited pepsin activity which should not be more than 20 %.

Based on the data provided in the table above, test and reference formulations are equivalent based on the quantitative comparison with respect to % decrease (inhibition) in pepsin activity.

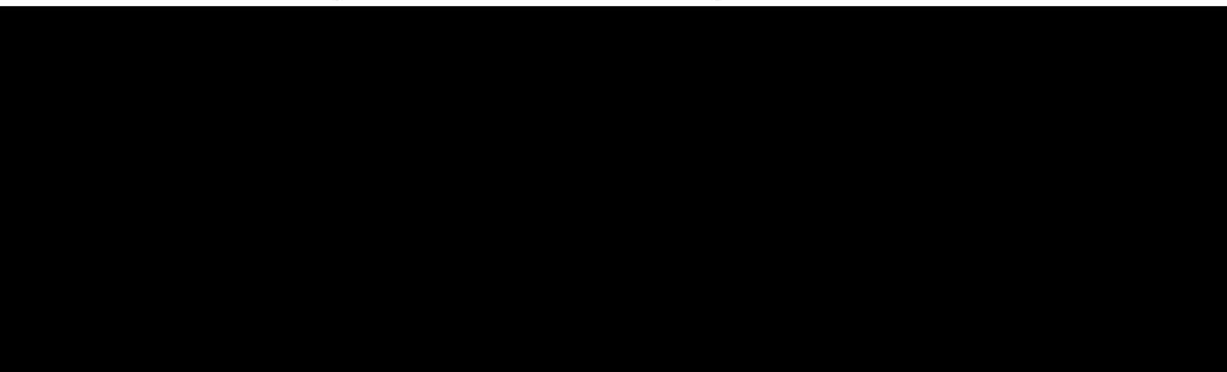
Conclusions on Bioassays of the Test and Reference Formulations

The data derived by the bioassays performed for sucralfate 1 g/5 ml Oral Suspension and the reference product Antepsin 1 g/5 ml oral suspension is summarised below:

- Test and reference products are similar in terms of kinetic profile.
- The test and reference products are bioequivalent in terms of Capacity Constant in both in vitro equilibrium binding study with bile salts and BSA.
- The test and reference products are bioequivalent in terms of inhibition of pepsin activity.

Therefore, test and reference products are considered bioequivalent.

2.5.2.1.2 In vitro equivalence studies with Antepsin Tablets



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A brief summary of the results is provided below.

A. *In vitro equilibrium binding study with Bovine Serum Albumin (BSA)*

The BSA binding profile of test/reference was compared and the affinity (k_1) and capacity (k_2) constants of the BSA was calculated using linear regression for test and reference products.

The 90 % CI for k_2 was calculated and T/R ratios were calculated for k_2 .

Table VI 90% CI for the Langmuir binding constant k_2 (Assessment of bioequivalence)

Parameter	Test	Reference	Ratio T/R	90 % CI	
	Mean			Lower	Upper
k ₂	235.2636	271.9428	86.51	83.60	89.42

The 90 % CI of ratio estimated by the Langmuir linear regression for capacity constant (k_2) was found to be within the set limits of the bioequivalence i.e., 80 % to 120 %. Therefore, the test and reference product are bioequivalent in terms of Capacity Constant.

B. *In vitro equilibrium binding study with bile salts*

The affinity (K_1) and capacity (K_2) constants of the total bile acids (GCA, GCDCA & TDCA) were determined using Langmuir equation for test and reference products. The 90 % CI for K_2 was calculated, and the Test/Reference ratios were calculated for K_2 .

Table VII 90 % CI for Test/Reference ratio for K_2 and mean T/R percent ratio for K_2 with linear regression (with acid pretreatment, pH 4.0).

Parameter	With acid pretreatment, pH 4.0			
	Mean Test (T)	Mean Reference (R)	Mean Test/Reference percent ratio (T/R)	90 % CI for Test/Reference ratio (Limit: 80%-120%)
Capacity Constant (K_2)	152.7096	156.9303	97.31	93.41-101.21

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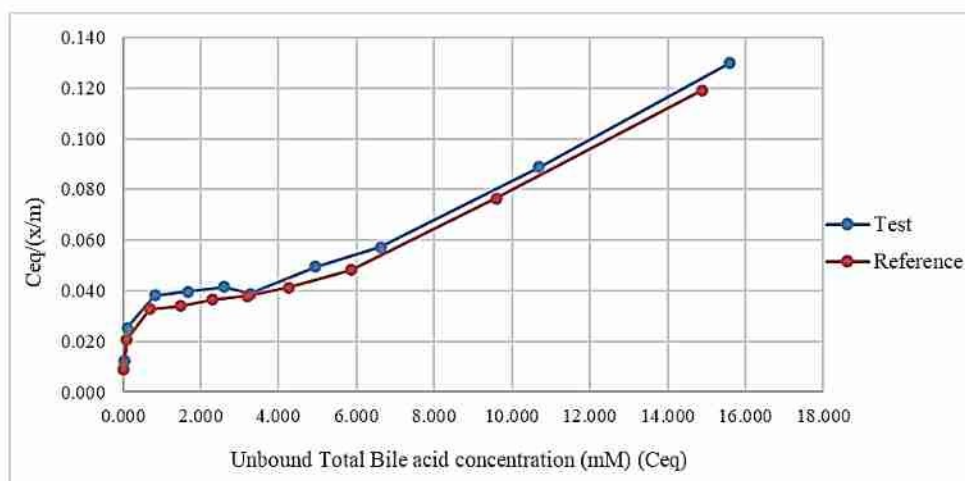


Figure 5 Langmuir plot of Test and Reference product at pH 4.0

The test and reference products are bioequivalent in terms of Capacity Constant.

C. *In vitro* kinetic binding study with bile salts

Based on the data generated in this kinetic study (for 0.5 mM and 40 mM concentrations):

1. The mean % binding of Bile acids to Test and Reference products was ranging from 74.277 to 97.055 and 75.420 to 96.529 at the 0.5 mM concentration respectively from 00.50 hr to 24.00 Hr.
2. The mean % binding of Bile acids to Test and Reference products was ranging from 46.060 to 58.870 and 48.643 to 61.931 at the 40 mM concentration respectively from 00.50 Hr to 24.00 Hr.
3. The mean binding capacity (x/m) (mM/g) to Test product and Reference product was ranging from 1.935 to 2.529 and 1.940 to 2.484 at the 0.5 mM concentrations respectively from 00.50 Hr to 24.00 Hr.
4. The mean binding capacity(x/m) (mM/g) to Test product and Reference product was ranging from 89.807 to 114.740 and 96.510 to 122.867 at the 40 mM concentrations respectively from 00.50 Hr to 24.00 Hr.
5. The results for 0.5 mM and 40 mM bile acid concentrations are as follows,
 - Unbound bile acids concentrations are similar
 - Bound bile acids concentrations are similar
 - Percent binding of bile acids to Sucralfate for test and reference products are found to be similar
 - Binding capacity of bile acids to Sucralfate for test and reference products is found to be similar
6. The obtained results indicate that the test product and reference product are similar in terms of kinetic profile.
7. The maximum binding was achieved in the range of 8.00 hr to 24.00 hrs for both test and reference products at constant bile acids concentration of 0.5 mM and 40 mM.

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D. *In vitro* enzyme (pepsin) activity study

The T/R ratio of % decrease/inhibition of pepsin activity at different sample concentrations of test and reference products is presented in the following table:

Table VIII Comparison of T/R ratios of % decrease in pepsin activity

Replicate	Sucralfate_1 45.00 mg/mL	Sucralfate_2 40.00 mg/mL	Sucralfate_3 30.00 mg/mL	Sucralfate_4 20.00 mg/mL	Sucralfate_5 10.00 mg/mL
1	63.42	64.52	75.75	69.70	50.14
2	63.35	64.56	75.64	68.92	49.64
3	62.84	63.15	74.62	67.13	46.37
4	63.46	63.39	73.92	66.30	47.35
5	65.59	68.96	79.53	74.29	62.17
6	64.76	68.54	79.90	73.96	60.85
7	78.65	85.04	100.24	103.45	115.05
8	78.25	84.45	99.85	101.91	110.08
9	76.55	83.19	98.41	98.22	112.32
10	76.22	83.21	98.05	97.36	109.47
11	55.74	56.93	66.10	66.42	49.37
12	55.79	57.54	66.76	65.25	47.71
N	12.00	12.00	12.00	12.00	12.00
Mean	67.05	70.29	82.40	79.41	71.71
SD	8.28	10.71	13.04	15.70	30.00
CV (%)	12.35	15.24	15.83	19.77	41.84

The T/R ratio for percent pepsin inhibition exceeded the 20 % difference threshold, however, as justified below, this difference is considered not clinically significant and does not compromise the therapeutic equivalence of the test product.

- Sucralfate's clinical therapeutic effect is produced by multiple complementary local mechanisms at the gastric/duodenal mucosal surface: (a) formation of an ulcer adherent proteinaceous complex (mucoadhesive barrier) that protects injured mucosa, (b) adsorption and reversible binding of pepsin reducing local proteolytic activity, (c) adsorption/interaction with bile salts, and (d) local buffering/neutralization effects and promotion of mucosal repair processes. The primary mechanism is the mucoadhesive barrier formation, while all other mechanisms are contributory. The pepsin inhibition endpoint represents only one mechanistic facet of sucralfate function and therefore cannot, predict overall clinical performance [24].
- The primary mechanism of action (acid-mediated gel formation and mucoadhesive barrier formation) and key contributory mechanisms (bile salt binding, protein binding) are preserved and equivalent between test and reference products. The comparable albumin binding is particularly relevant, as albumin binding serves as a surrogate for sucralfate's interaction with exposed proteins at the ulcer base and mucosa. These data indicate that the test product retains full capacity to form the sucralfate-protein complex that underlies the

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protective mucosal coating. McQuaid and Isenberg (1992) reviewed the medical therapy of peptic ulcer disease and concluded that sucralfate's efficacy is attributable to its "unique mechanism of action involving formation of a protective barrier at the ulcer site," with pepsin binding being a secondary contributory factor [25].

- The replicate heterogeneity observed in the pepsin inhibition data is consistent with method-related variability rather than true differences in the intrinsic pepsin inhibition capacity of the test product. The range observed is below 80% for 4 out of 5 concentrations tested and could be due to the below attributes.
 - pH-dependent polymerization of sucralfate
 - Sensitivity of pepsin enzyme activity
 - Non-linear inhibition kinetics
 - Surface adsorption and matrix effects

An additional comparison of the reference sucralfate oral suspension and reference sucralfate tablet was performed: the mean T/R ratios performed at 5 different concentrations (n=12) of % decrease in pepsin activity between reference suspension and reference tablet were also observed to be in overlapping range (66.74-82.13 %) as that of test suspension versus reference tablet. Since the Reference suspension product did not achieve the theoretical target range when compared with the reference tablet, the expected acceptance criterion of 80 to 120% is not considered appropriate for this functional method. Due to the overlapping range of T/R ratios observed between test suspension and reference suspension when compared against reference tablet, the test suspension can be considered as equivalent to the reference product.

The results show similarity, thereby establishing a second bridge with another reference product from the European market. The full studies reports are provided in updated Module 5.

E. Sameness of Active Pharmaceutical Ingredient

A comparison with Antepsin tablets was further made between comparative physicochemical properties and the API of the products. The following parameters were assessed:

API composition

- API composition: sucrose octasulfate and aluminium content
- C, H, S, Al by elemental analysis on Test API, C/S ratio and C/Al ratio
- Acid neutralizing capacity
- Spectroscopic characterizations, such as FT-IR, UV, solid state ²⁷Al NMR, DSC, TGA and powder X-ray diffraction PXRD.

Comparative acid neutralizing capacity

- Acid neutralizing capacity
- Comparative dissolution, aluminium release

The suspension exhibited similar behaviour

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The data derived from the above analyses are provided as Supplementary Analysis of the Pharmaceutical Equivalence Study Report in Module 3.2.P.2. The additional analysis demonstrates that the suspension product is also comparable with reference sucralfate tablet product.

2.5.2.1.3 Comparison with published literature

2.5.2.1.3.1 Literature Data of Italian Antepsin Suspension

Since a direct GMA cannot be established, although strongly assumed, the Applicant proceeded with seeking confirmation that the Italian comparator product was used in clinical trials reported in scientific literature.

The applicant reviewed Italian clinical trials and corresponded with the investigators to verify the specific sucralfate formulation used. The outcome is reported in the table below. Due to the old nature of the active substance and the published studies, most of the authors have either passed away or could not confirm, nor deny, that Antepsin was used in the published study.

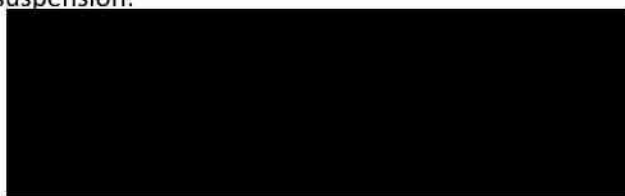
Table IX Communication with authors

Article	Author	Response	Confirmation for sucralfate product

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Article	Author	Response	Confirmation for sucralfate product
[REDACTED]			

While it is not possible to provide direct confirmation that the exact comparator product included in the dossier was used in the referenced clinical studies, it is reasonable to assume that it was used, at least in part, in several of the aforementioned studies, given that the product was first approved in Italy in 1991. Accordingly, with the exception of the study by [REDACTED], it is likely that this product was used in the subsequent studies, all of which explicitly report the use of sucralfate suspension:



In summary, one study [REDACTED] [18] has been definitively confirmed to have utilized this product. Three additional Italian studies ([REDACTED] [21]) are considered likely to have used the same product, based on the country of publication and the relevant timeframe; however, independent confirmation could not be obtained.

2.5.2.1.3.2 *Literature Data of Danish Antepsin tablets*



Antepsin as referenced in older literature (e.g., formulations cited as “Antepsin, Famos”) and Antepsin currently registered/marketed in Denmark under Orion are commercially and historically linked. Famos originally manufactured/supplied Antepsin and was acquired by Orion in 1988, with the merge completed in 1993, after which the product continued in Orion’s portfolio and is the marketed Antepsin product in Denmark [27]. For regulatory/bridging purposes, it is therefore reasonable to treat the Danish Antepsin product cited in the literature as the same brand family that is now marketed under Orion.

In short, the following studies were conducted with Antepsin Famos tablets and reported in Literature. All studies were conducted either in Denmark or in Sweden.

Table X Studies conducted with the Danish product Antepsin

Study	Country	Product	Dose	N of subjects and Design	Pivotal study	Relevance
<i>Duodenal Ulcer</i>						

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Study	Country	Product	Dose	N of subjects and Design
	Sweden	Andapsin@, Farmos Group AB (tablets)	1 g four times daily	371 patients multi-centre randomized double-blind trial sucralfate vs cimetidine
	Denmark	Sucralfate of Farmos A/S, Glostrup, Denmark	2 g at bedtime 1 g four times daily	77 patients randomized controlled trial sucralfate vs placebo
<i>Gastric Ulcer</i>				
	Sweden	Sucralfate (Andapsin® Farmos Group AB)	1 g four times daily	134 patients multi-centre, double blind randomized prospective trial sucralfate vs cimetidine
<i>Prevention of Recurrences of Gastric Ulcer</i>				
	Denmark	500 mg sucralfate tablets (Farmos Group)	2 g twice daily	104 patients multicentre, double blind, randomised trial sucralfate vs omeprazole
	Denmark	Sucralfate Farmos A/S, Copenhagen, Denmark	2 g twice daily	70 patients Double blind, placebo-controlled study

There is also another study by [REDACTED]. In this study one hundred and two patients, who obtained relief from their duodenal ulcer symptoms with sucralfate (Antepsin R) in a dosage of 2 g b.i.d. for four weeks. Although the Antepsin product was evaluated, there is no reference on the dosage form used.

Therefore, a second bridge with a product used in literature is established.

Having established the pharmaceutical equivalence and comparable in vitro performance of the product under assessment to the reference product Antepsin® 1 g/5 ml Oral Suspension, this comparability is extended to the products used in the submitted publications. The demonstrated

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equivalence to the marketed Italian product allows for a reliable bridge to the products used in the key historical literature.

A brief description of the products used in the published literature and respective doses for each indication is provided in the below table.

The relevance of each product used in the studies listed in the table below is as follows:

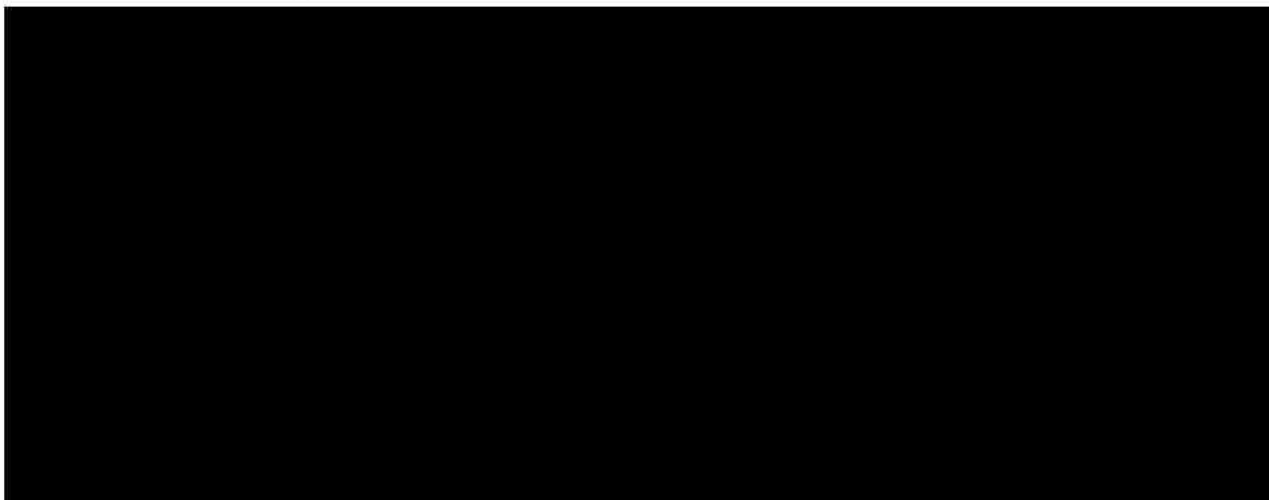


Table XI Sucralfate products used in efficacy studies

Study	Product	Dose	N of subjects and Design	
<i>Duodenal Ulcer</i>				
	Ulsanic tablets (Aspen Pharmaceuticals, South Africa)	2 g (two tablets) four times daily	65 patients double-blind randomized trial sucralfate vs placebo	
	Andapsin@, Farmos Group AB (tablets)	1 g four times daily	371 patients multi-centre randomized double-blind trial sucralfate vs cimetidine	
	Sucralfate 500 mg tablets (Nordic Laboratories Inc., Canada,	two tablets of 500 mg four times daily	59 patients double-blind randomized trial sucralfate vs cimetidine	
	Sucralfate (product not stated)	1 g, 30 min before each meal and at bedtime	70 patients randomized, double-blind, controlled trial sucralfate vs cimetidine	
	Sucralfate 1 g tablets (details not reported)	1 g one hour before the three daily meals and one hour before bedtime	61 patients randomized, double-blind, double-placebo trial sucralfate, cimetidine, or a combination of both.	
	Sucralfate emulsion of Hexal Pharma Germany	1 g four times daily	85 patients randomized with blind observer trial sucralfate vs ranitidine	
	Sucralfate (product not stated)	1 g half an hour before breakfast, lunch, and dinner, and at bedtime	283 patients randomized single-blind, single centre sucralfate vs cimetidine	
	Sucralfate (product not stated)	1 g three times a day and at bedtime	50 patients randomized trial sucralfate vs cimetidine	

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Study	Product	Dose	N of subjects and Design
	Sucralfate (product not stated)	two 500 mg tablets on waking, 1 hour before lunch and supper and before bed	112 patients randomized controlled trial sucralfate vs cimetidine
	Sucralfate tablets of Chugai Pharmaceutical Co. Ltd.	1 g four times daily	101 patients randomized single-blind trial sucralfate vs ranitidine
	Sucralfate (product not stated)	1 g four times daily	67 patients randomized controlled trial sucralfate vs ranitidine
	Sucralfate 1 g tablets (details not reported)	1 g four times daily	165 patients multi-centre randomized double-blind trial sucralfate vs ranitidine
	Sucralfate of Farmos A/S, Glostrup, Denmark	2 g at bedtime 1 g four times daily	77 patients randomized controlled trial sucralfate vs placebo
	Sucralfate tablets (details not reported)	2 g twice daily	347 patients 2 double blind randomized double blind parallel group, multi centre trials. sucralfate vs placebo
	Sucralfate (product not stated)	1 g four times daily (before each meal and at bedtime).	667 patients randomized multi centre comparative clinical trial sucralfate vs cimetidine
	Sucralfate suspension (details not reported)	1 g four times daily	293 patients randomized double-blind placebo-controlled parallel group multi-centre trial sucralfate vs placebo
	Sucralfate tablets (details not reported)	1 g four times daily (30 minutes before meals and at bedtime) or two	222 patients multi centre, randomized, prospective, open-label pragmatic trial with two parallel groups

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Study	Product	Dose	N of subjects and Design
		tablets (1 g) twice daily (30 minutes before breakfast and at bedtime)	sucralfate (four doses) versus sucralfate (two doses)
	Sucralfate (product not stated)	1 g four times daily	114 patients prospective randomized trial sucralfate/ metronidazole/ clarithromycin vs omeprazole
Maintenance therapy for Duodenal Ulcer			
	Sucralfate tablets (details not reported)	4 g daily	59 patients double blind placebo-controlled trial sucralfate vs placebo
	Sucralfate tablets (details not reported)	1 g twice daily	88 patients double blind placebo-controlled trial sucralfate vs placebo
	Sucralfate 1 g tablets (details not reported)	1 g twice daily	84 patients double blind placebo-controlled trial
	Sucralfate (product not stated)	2 g daily	117 patients randomized double blind controlled trial sucralfate vs placebo vs cimetidine
	Sucralfate tablets (details not reported)	1 g twice daily	254 patients randomized placebo-controlled parallel group trial sucralfate vs placebo
	Sucralfate (product not stated)	1 g four times daily	46 patients randomized controlled study sucralfate vs cimetidine
	Sucralfate (product not stated)	2 g daily	71 patients single blind randomized multi-centre trial sucralfate vs cimetidine
	Sucralfate (product not stated)	2 g daily	59 patients randomized trial sucralfate vs ranitidine

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Study	Product	Dose	N of subjects and Design
	Sucralfate 1 g tablets (details not reported)	2 g daily	254 patients double-blind, randomized, placebo- controlled, parallel groups, multi-centre trial sucralfate vs placebo
	No treatment; Triact Tab 2, 1 hour after meals three times a day (each tablet containing 200 mg aluminium hydroxide, 150 mg magnesium trisilicate, and 25 mg simethicone [Regent Lab., London, UK] with a neutralizing capacity of 80 mmol/day); Trimipramine maleate, 25 mg at night (May & Baker, Bournemouth, UK); Pirenzepine 50 mg at night (Boehringer Ingelheim, Mannheim, West Germany); Cimetidine (Smith Kline & French Laboratories, Philadelphia, PA) 200 mg at night; Cimetidine 400 mg at night; Ranitidine 150 mg at night (Glaxo Co. Ltd., Greenford, UK); Sucralfate 1 g (Chugai Pharmaceutical Co., Tokyo, Japan) between breakfast and lunch, and at night.		787 patients randomized controlled trial
	Sucralfate 1 g tablet (details not reported)	2 g twice daily	21 patients randomized controlled trial sucralfate vs omeprazole vs Maalox
	Sucralfate (product not stated)	1 g four times daily	46 patients randomized trial sucralfate vs cimetidine
	Sucralfate (E. Merck, Darmstadt, West Germany) 1 g	1 g four times daily	75 patients randomized, double-blind, double-dummy design sucralfate vs ranitidine
Gastric Ulcer			

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Study	Product	Dose	N of subjects and Design
	Sucralfate granules (Chugai Pharmaceutical Co., Ltd.)	900 mg once daily	138 patients randomized double-blind, placebo-controlled trial sucralfate vs placebo
	Sucralfate (Andapsin® Farmos Group AB)	1 g four times daily	134 patients multi-centre, double blind randomized prospective trial sucralfate vs cimetidine
	Sucralfate (product not stated)	2 g twice daily	76 patients double-blind, randomized trial sucralfate vs cimetidine vs placebo
	Sucralfate tablets (Ulsanic)	Two 500 mg tablets on waking, 1 hour before lunch and supper and before bed	112 patients randomized controlled trial sucralfate vs cimetidine
	Sucralfate (product not stated)	1 g four times daily	667 patients multi centre double blind randomized trial sucralfate vs cimetidine
	Sucralfate (product not stated)	1 g four times daily	60 patients open, randomized, prospective, comparative study trial sucralfate vs ranitidine
	Sucralfate 1 g/5 ml suspension (details not reported)	4 g daily	160 patients randomized controlled multi-centre trial sucralfate vs ranitidine
	Sucralfate tablets (Ulsanic)	1 g four times daily	52 patients double-blind, randomized, and prospective. sucralfate vs placebo
	Sucralfate granules (details not reported)	2 g, twice daily and 1 g, four times daily	57 patients randomized, single-blind trial sucralfate different doses

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Study	Product	Dose	N of subjects and Design
	Sucralfate tablets (details not reported)	2 g daily	290 patients multi-centre, prospective, randomized, open, long-term trial sucralfate vs ranitidine
	Sucralfate liquid (details not reported)	2 g twice daily	64 patients multi-centre randomized double-blind prospective comparative trial sucralfate vs ranitidine
Prevention of Recurrences of Gastric Ulcer			
	Sucralfate (product not stated)	1 g four times daily	60 patients open, randomized, prospective, comparative study trial sucralfate vs ranitidine
	Sucralfate tablets (details not reported)	1 g in the morning and 2 g at night	72 patients randomized placebo-controlled trial sucralfate vs placebo
	Sucralfate 250 mg tablets (Chugai Pharmaceutical Co, Japan)	1 g three times daily	363 patients randomized placebo-controlled trial sucralfate vs placebo
	500 mg sucralfate tablets (Farnos Group)	2 g twice daily	104 patients multicentre, double blind, randomised trial sucralfate vs omeprazole
Gastrointestinal Bleeding			
	Sucralfate tablets dissolved in water (URBAL of Merck Mollet de Valles, Spain)	0.5 to 1 g four times daily	72 patients Prospective, randomized, controlled trial sucralfate vs no treatment vs antacid vs ranitidine)
	Sucralfate in solution (details not reported)	1 g four times daily	139 patients prospective, randomized trial sucralfate vs cimetidine

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Study	Product	Dose	N of subjects and Design
<i>Esophagitis</i>			
	Sucralfate suspension (details not reported)	6 g/day	98 patients double-blind, multi-centre, endoscopically controlled trial sucralfate vs ranitidine
	Sucralfate granules (details not reported)	1 g four times daily	20 patients double-blind controlled study with two parallel groups. sucralfate vs ranitidine
	Sucralfate tablets (details not reported)	4 g four times daily	41 patients randomized, prospective, single-blind, crossover therapeutic trial sucralfate vs cimetidine
	Sucralfate suspension (details not reported)	1 g four times daily	49 patients multi-centre randomized controlled study sucralfate vs ranitidine
	Sucralfate suspension (in sachets) (details not reported)	1 g four times daily	42 patients single-blind randomized multi-centre study sucralfate vs cimetidine
	Ulcir 1 g sachet Laboratoires Houde (SANOFI WINTHROP INDUSTRIE, France)	1 g four times daily	50 patients double-blind study sucralfate vs alginate/antacid
	Sucralfate powder for suspension (Antepsin®)	1 g four times daily	68 patients randomized, double-blind study sucralfate vs alginate/antacid (Gaviscon)
	Sucralfate sachet (powder to be suspended in water) (details not reported)	1 g four times daily	16 patients randomized single-blind study sucralfate vs famotidine
	Sucralfate suspension (details not reported)	1 g four times daily	70 patients double-blind multi-centre, randomized study

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Study	Product	Dose	N of subjects and Design
			sucralfate + placebo vs sucralfate + cimetidine
	Sucralfate granules (details not reported)	1 g four times daily	66 patients multi-centre placebo-controlled double-blind study sucralfate vs placebo
	Sucralfate granules 1 g in suspension (Keal, 1 g sachet; Pierre Fabre Medicament, Paris, France)	1 g four times daily	45 patients randomized study sucralfate vs antacid suspension (aluminium hydroxide gel 240 mg, magnesium hydroxide paste 133.2 mg/1000 mg) 1.5 ml four times daily
	Sucralfate gel 1 g (details not reported)	1 g twice daily	139 patients randomized, double-blind, placebo-controlled study sucralfate vs placebo
	Sucralfate suspension (details not reported)	1 g four times daily	75 patients double-blind, multi-centre, randomized study sucralfate vs sucralfate + ranitidine
Combined Therapy with H₂-Antagonist Drugs			
	Sucralfate (Ulcogant)	1 g six times daily	32 patients randomized study sucralfate vs ranitidine
	Sucralfate (product not stated)	1 g every 6 hours (NG tube)	104 patients retrospective study sucralfate vs cimetidine
	Sucralfate (Ulcogant, Merck and Co., Zurich, Switzerland) Suspension	1 g six times daily	244 patients randomized controlled trial sucralfate vs antacid vs ranitidine
	Sucralfate suspended to water (product not stated)	1 g four times daily	130 patients randomized study sucralfate vs antacids, h ₂ blockers

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Study	Product	Dose	N of subjects and Design
	Sucralfate (product not stated)	1 g six times daily	100 patients prospective, controlled, randomized study sucralfate vs cimetidine
	Sucralfate (NG tubes) (product not stated)	1 g four times daily	98 patients prospective, randomized, open trial sucralfate vs ranitidine + antacids
	Sucralfate 1 g suspended in 20 mL of water (details not reported)	1 g four times daily (NG Tube)	96 patients randomized trial sucralfate vs cimetidine
	Sucralfate 1 g suspension (Ulcogant, Fa. E. Merck, Darmstadt, Federal Republic of Germany)	1 g four times daily	100 patients prospective, controlled, randomized study sucralfate vs antacid
	Sucralfate suspended in water (details not reported)	1 g four times daily (NG Tube)	114 patients prospective randomized study sucralfate vs cimetidine
	Sucralfate suspension (1 g/5 ml) (details not reported)	1 g four times daily (NG tube)	60 patients randomized study sucralfate vs ranitidine
	Sucralfate suspension (Sulcrate, Hoechst Marion Roussel)	1 g four times daily (NG tube)	1,200 patients multi-centre, randomized, blinded, placebo-controlled trial sucralfate vs ranitidine
	Sucralfate suspension (Hoechst Marion Roussel Inc)	1 g four times daily (NG tube)	140 patients randomized, double-blind, double-sham study sucralfate vs antacids
Miscellaneous Uses			
	Sucralfate 1-g tablet (details not reported)	1 g four times daily	143 patients randomized, double-blind trial sucralfate vs placebo
	Sucralfate 500 mg tablet (Mukal, Delta, Iceland)	2 g twice daily	16 patients randomized double-blind crossover study

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Study	Product	Dose	N of subjects and Design	
			sucralfate vs placebo	
	Sucralfate suspension (details not reported)	2 g twice daily	50 patients randomized, double-blind, placebo-controlled, multi-centre study sucralfate vs placebo	
	Sucralfate granules (details not reported)	1 g four times daily	138 patients randomized study sucralfate vs placebo	
	Sucralfate (product not stated)	1 g four times daily	45 patients double blind randomized study sucralfate vs placebo	
	Sucralfate suspension (1 g/10ml) (details not reported)	1 g four times daily	19 patients double-blind randomized trial sucralfate vs placebo	
	Sucralfate (product not stated)	1 g three times daily	331 patients randomized multi-centre sucralfate vs ranitidine	
	Sucralfate suspension (Chugai)	2 g twice daily 1 g four times daily	24 patients double blind, placebo controlled, crossover comparison with randomisation sucralfate vs placebo	

The above data strongly support a reliable bridge to the products used in the published studies.

The detailed description of efficacy of the below products is provided in paragraph 2.5.4 (OVERVIEW OF EFFICACY) of the present document.

2.5.2.1.4 Positioning within the established "Formulation Space"

To further solidify the scientific bridge between the product under assessment, Sucralfate 1 g/5 ml Oral Suspension, and the products cited in the bibliographic data, an analysis of the overall "formulation space" for sucralfate products that have demonstrated clinical efficacy has been conducted. The analysis is based on release characteristics, BCS class, formulation type, excipients, regimen, etc., as indicated by the EMA Clinical pharmacology and pharmacokinetics: questions and answers (Q9 "Well-established use, 1.2. Bridging requirements), since the Agency recognises that well-established use applications often rely on:

- Older clinical studies,
- Products that are no longer on the market, and
- Incomplete information on the exact historical formulations.

In such cases, EMA advises that applicants may define a "formulation space" based on products that have demonstrated clinical efficacy and safety and then position the proposed product within this space.

Key elements in defining this formulation space include:

- Formulation type (e.g. immediate release tablet, oral suspension),
- BCS class and relevance to local/systemic action,
- Release characteristics (e.g. dissolution, disintegration),
- Qualitative/quantitative excipient patterns, and
- Dose and regimen used in the literature.

The regulatory principle is that, where a proposed product lies clearly within such a formulation space – and there is no plausible reason to expect clinically relevant differences – the existing literature data can be extrapolated without requiring product specific clinical trials.

Considering that sucralfate is a very old active substance and that most of the pivotal literature derives from the 1980s and 1990s, the Applicant considers that the EMA "formulation space" approach offers a pragmatic, scientifically robust framework that is directly transferable to the present UK context under the WEU legal basis. The Applicant therefore respectfully invites the MHRA to apply the same formulation space principle in this case: the proposed Sucralfate 1 g/5 ml Oral Suspension has been shown to lie clearly within the established sucralfate formulation space, and there is no scientifically plausible basis to expect clinically relevant differences compared with the products used in the historic literature. On this basis, extrapolation of the existing literature data to the proposed product, without additional product specific clinical trials, is justified and consistent with both EMA's established practice and MHRA's own risk proportionate approach to WEU applications.

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2.5.2.1.4.1 *Application of the formulation space*

In line with the concept of formulation space, the Applicant has:

1. Identified the range of sucralfate formulations (tablets and suspensions) with documented clinical efficacy in the literature; and
2. Analysed their formulation characteristics, excipients, dose, regimen and performance to define an overall "sucralfate formulation space".

For sucralfate:

- BCS classification and its relevance

Sucralfate is typically considered a BCS Class IV substance (low solubility, low permeability). However, for a locally acting, non-systemic drug like sucralfate, this classification must be interpreted in context. Low permeability is, in fact, a prerequisite for its mechanism of action, as it ensures the drug remains at the site of action in the GI tract. While solubility is low in neutral pH, the critical attribute is its reactivity and polymerization in the low pH environment of the stomach. Therefore, the traditional BCS framework is less relevant than in vitro performance under biorelevant acidic conditions."

- Formulation type

A review of the submitted literature (see Table XI) reveals that efficacy has been established across two primary formulation types:

- *Immediate-Release Tablets*: This is the most common formulation, used in the majority of pivotal studies. These rely on rapid tablet disintegration to release sucralfate powder.
- *Oral Suspensions*: Several studies have also demonstrated efficacy using oral suspensions. These formulations represent the most rapid delivery, as the sucralfate is already in a finely dispersed state.

The product under assessment is in the form of oral suspension. Several suspension formulations have been assessed in the literature. The marketed product used in the in vitro equivalence studies (Chugai Pharmaceutical Co.) has been evaluated in the studies of [REDACTED]. Sucralfate in the form of oral suspension has been used in several other studies listed in Table XI above. However, the details of these products are not reported.

- Excipients

The excipients used in the product under assessment are provided in the below table. While detailed excipient lists for most of the products used in publications listed above are unavailable, it is scientifically sound to assume they were manufactured using excipients commonly used in the pharmaceutical industry (e.g., binders, fillers, disintegrants, lubricants).

A comparison among the excipients employed in the proposed formulation and the known products used in the literature is provided below:

Sucralfate 1 g/5 ml Oral Suspension

Table XII Comparison of composition of sucralfate products

Glycerol	Glycerol	Glycerol	Glycerol	-	-	-	Glycerol	-
Sodium dihydrogen phosphate dihydrate	Sodium dihydrogen phosphate dihydrate	Sodium phosphate	Sodium dihydrogen phosphate dihydrate	-	-	-	Sodium monobasic phosphate dihydrate,	-
Sodium methyl paraben	Sodium methylparaben	Sodium methylparaben	Sodium methyl hydroxybenzoate (E219)	-	-	-	Sodium methyl methylparaben,	Sodium methylparaben
Xanthan gum	Xanthan gum	Xanthan gum	Xanthan gum	-	-	-	Xanthan gum	
Saccharin sodium	Sodium saccharin dihydrate		Saccharin sodium	-	-	-	Sodium saccharin	Sodium saccharin
Aniseed	Anise flavour,		Aniseed flavour	-	-	-	Anise flavour	
Caramel	Caramel flavour	Caramel-flavour	Caramel flavour	-	-	-	Caramel flavour	
Water purified	Purified water		Purified water	-	-	-	Purified water	Purified water
-	Sodium propylparaben	Sodium propylparaben	Sodium propyl hydroxybenzoate (E217)	-	-	-	Sodium propyl Propylparaben	Sodium propylparaben
-	-	-	-	Macrogol 6000	Macrogol 6000	Macrogol 6000	-	Guar gum
-	-	-	-	Microcrystalline cellulose	Microcrystalline cellulose	Microcrystalline cellulose	-	Sorbitol
-	-	-	-	Calcium Carmellose	Calcium Carmellose	Calcium Carmellose	-	Sorbic acid
-	-	-	-	Magnesium stearate.	Magnesium stearate.	Magnesium stearate.	-	Flavour 26G55

The function of excipients differs between tablets and suspensions. In tablet formulations, the excipients ensure disintegration and in suspension formulations the excipients ensure dose uniformity, stability, and palatability. This includes suspending agents (e.g., xanthan gum, glycerol), wetting agents, preservatives, and flavouring agents.

The excipients used in oral suspensions are standard, inert, and their primary function is to guarantee that the correct dose of uniformly dispersed sucralfate particles is delivered with each administration. There is no evidence that these common pharmaceutical-grade excipients interfere with sucralfate's acid reactivity.

The excipients in the product under assessment are standard for a modern oral suspension. They ensure the physical stability and accurate delivery of the product, which are the critical functions required. They are functionally equivalent to the excipients used in other effective suspension formulations (used in the literature data above).

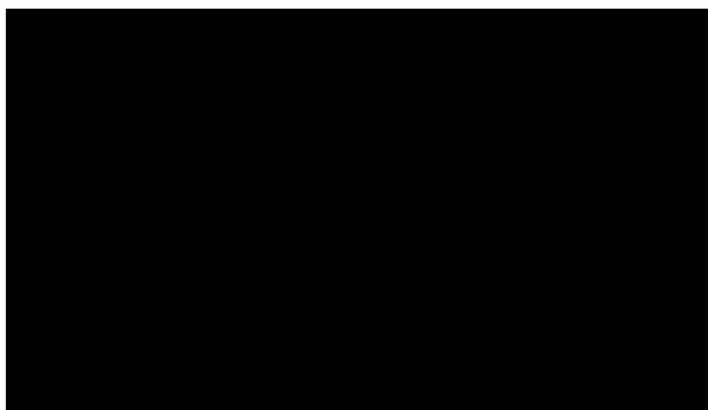
- Dosage Regimen

The submitted literature establishes efficacy for sucralfate 1g tablets across multiple regimens, most commonly 1 g four times daily. The proposed posology for the product under assessment is consistent with these reported in the literature, ensuring the product will be used in a manner proven to be effective.

The equivalence between sucralfate suspension and tablets, as shown in the previous comparison, further strengthens the concept of the wide formulation space for sucralfate immediate release dosage forms, as long as the products are formulated with conventional excipients for immediate release dosage forms and they ensure the availability of reactive sucralfate in the acidic gastric environment.

2.5.2.1.5 Safety Assessment

The EU available suspension products containing glycerol, sodium methyl and sodium propyl parahydroxybenzoate, saccharin sodium, sodium dihydrogen phosphate dihydrate, xanthan gum, caramel aroma, anise aroma, and purified water are the following:



All other suspension products list in table below, exhibit different composition.

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Table XIII Qualitative composition of EU approved sucralfate suspensions

Product	Excipients
Crafilm (Sospensione per uso orale) (IT)	Carrageenan, potassium sorbate, sorbitol, aspartame, flavour cream, flavour vanilla, flavour lemon, povidone, purified water
Peptonorm 1000 mg/5 ml Oral suspension (GR)	Glycerol, sodium methylparaben, sodium propylparaben, sodium phosphate monobasic, xanthan gum, aroma cherry brandy, purified water
Sucralfaat Sandoz suspensie 1, suspensie voor oraal gebruik 1 g (NL)	Glycerol, methyl 4-hydroxybenzoate, propyl 4-hydroxybenzoate, sorbitol, chlorhexidine diacetate, aluminum chloride, sodium cyclamate, xanthan gum, sodium citrate, water
Sucralfato Mylan 1000 mg/5 ml, Suspensão oral (PT)	Sorbitol, methylparaben, methylhydroxyethylcellulose, pure crystallized citric acid, sodium cyclamate, sodium saccharin, glyceryl monostearate, dimethicone, aroma grapefruit, purified water, ethanol
Ulgastran, 1 g/5 ml, zawiesina doustna (PL)	Glycerol, methyl parahydroxybenzoate, propyl parahydroxybenzoate, saccharin sodium, hypromellose, simethicone emulsion 30%, sorbitol, citric acid, vanillin, lemon oil, purified water

The composition of the product under assessment and Antepsin suspension is presented in the following table:

Table XIV Composition of sucralfate 1 g/5 ml oral suspension and Antepsin suspension

Component	Function	Antepsin 1 g/5 ml Oral Suspension
Sucralfate	Active ingredient	
Glycerol	Humectant	
Sodium dihydrogen phosphate dihydrate	Buffering agent	
Sodium methyl parahydroxybenzoate	Preservative	
Sodium propyl parahydroxybenzoate	Preservative	
Xanthan gum	Thickener	
Saccharin sodium	Sweetener	Not calculated
Aniseed	Flavour	Not calculated
Caramel	Flavour	Not calculated
Water, purified	Solvent	-

The excipients employed in the proposed suspension formulation are well known and commonly used in the pharmaceutical industry. As seen on the table above, with the exception of sodium propyl parahydroxybenzoate which has not employed in the product under assessment, the qualitative composition of the two products is similar. The reverse engineering activities performed by the applicant on Antepsin 1 g/5 ml oral suspension included the quantitation of glycerol, sodium

2.5 Clinical overview

dihydrogen phosphate dihydrate, Sodium propyl hydroxybenzoate and Sodium methyl hydroxybenzoate. The results provided in Table XIV above indicate that the minor quantitative variation identified for glycerol and sodium methyl parahydroxybenzoate is unlikely to affect the in vivo performance of the drug product.

Xanthan gum is widely used in oral pharmaceutical formulations as suspending and thickening agent. Any potential quantitative differences with the reference product are not expected to affect the in vivo performance of sucralfate. Furthermore, the quantity of sodium saccharin in the proposed product is negligible. Any variation on saccharin concentration of the reference product is not expected to result in different in vivo performance of sucralfate.

The safety justification for the proposed composition is based on the following grounds:

- No novel excipients: All excipients in the test product are widely used in oral suspensions. Each is listed in the FDA Inactive Ingredient Database and/or EU databases for the oral route at levels at or above those proposed in our product.
- Functional equivalence: The excipients were selected to ensure comparable pH, osmolality, viscosity, palatability, and product stability, without introducing new toxicological concerns.
- Exposure within established limits: For each excipient that differs from the reference product, the maximum daily patient exposure at the maximum recommended daily dose has been calculated.
- Preservative system: Preservative levels are below thresholds associated with safety concerns for the intended population.
- Labelling: the composition against the EU “Excipients in the label and package leaflet” guideline and FDA recommendations have been assessed.
- Comparative product performance: The test product is comparable to the reference product in critical attributes (pH, osmolality, viscosity, density, and organoleptic profile) within predefined acceptance criteria, supporting comparable local tolerability.

In summary, the excipient differences are justified based on function, quality, and exposure well within established safety limits for the oral route. No additional safety risk is anticipated for the proposed preparation.

The detailed safety profile of the excipients listed in Table XIV is presented below:

2.5.2.1.5.1 Glycerol

Glycerin, also known as glycerol, is used as an antimicrobial preservative, cosolvent and sweetening agent [108].

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 [109]. 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 [110]. Slower administration has no deleterious effects [111]. Glycerol may also be used orally in doses of 1.0-

2.5 Clinical overview

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 [112]:

- LD₅₀ (Guinea pig, Oral): 7.75 g/kg
- LD₅₀ (Mouse, IP): 8.70 g/kg
- LD₅₀ (Mouse, IV): 4.25 g/kg
- LD₅₀ (Mouse, Oral): 4.1 g/kg
- LD₅₀ (Mouse, SC): 0.09 g/kg
- LD₅₀ (Rabbit, IV): 0.05 g/kg
- LD₅₀ (Rabbit, Oral): 27 g/kg
- LD₅₀ (Rat, IP): 4.42 g/kg
- LD₅₀ (Rat, Oral): 5.57 g/kg
- LD₅₀ (Rat, Oral): 12.6 g/kg
- LD₅₀ (Rat, SC): 0.1 g/kg

Glycerol is of very low acute toxicity to mammals. The range of acute oral LD₅₀ 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 LD₅₀ 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 [113].

Mild osmotic diuresis occurs after oral glycerol doses of 1.0-1.3 g glycerol/kg bw [114]. 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 [115].

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).

2.5.2.1.5.2 Sodium dihydrogen phosphate dihydrate

Monobasic sodium phosphate is widely used as an excipient in parenteral, oral, and topical pharmaceutical formulations [116].

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 [117] virtually unknown except in certain disease states [118] or in patients

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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 [119-121]. 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 [122]:

- LD₅₀ (Rat, IM): 250 mg/kg
- LD₅₀ (Rat, Oral): 8,290 mg/kg

The WHO tolerable daily intake for phosphorus is 70 mg per kg of body weight [123]. At the maximum daily sucralfate dose of 8 g (40 mL of the oral suspension), this 70 mg/kg bw limit is not exceeded.

2.5.2.1.5.3 Sodium methyl parahydroxybenzoate

Sodium methyl hydroxybenzoate (methylparaben) and other parabens are widely used as antimicrobial preservatives in cosmetics and oral and topical pharmaceutical formulations [124]. 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 [125-127]. Delayed-contact dermatitis occurs more frequently when parabens are used topically, but has also been reported to occur after oral administration [128, 129]. 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 [130]. 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 [131]. The WHO has set an estimated total acceptable daily intake for methyl-, ethyl-, and propylparabens at up to 10 mg/kg bodyweight [132].

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

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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 [133]

- LD₅₀ (Dog, Oral): 3.0 g/kg
- LD₅₀ (Mouse, IP): 0.96 g/kg
- LD₅₀ (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' [REDACTED]

2.5.2.1.5.4 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 [134].

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.

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) [134].

Reported toxicity data [134-136]:

- LD₅₀ (Dog, Oral): > 20 g/kg
- LD₅₀ (Rat, Oral): > 45 g/kg
- LD₅₀ (Mouse, Oral): > 1 g/kg
- LD₅₀ (Mouse, IP): > 50 mg/kg
- LD₅₀ (Mouse, IV): 100-250 mg/kg

The estimated acceptable daily intake for xanthan gum has been set by the WHO at up to 10 mg/kg body-weight [136]. Given the maximum daily intake of sucralfate (8 grams of sucralfate or 40 ml of suspension) and the concentration of xanthan gum 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.

2.5.2.1.5.5 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 [137, 138];. It is also used in vitamin preparations.

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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 [137].

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 [139]. 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 [140].

Reported toxicity data [141]:

- LD₅₀ (Mouse, Oral): 17.5 g/kg
- LD₅₀ (Rat, IP): 7.1 g/kg
- LD₅₀ (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] 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.

2.5.2.1.5.6 *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.

2.5.2.1.5.7 *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.

2.5.2.2 **DOSAGE FORM/STRENGTH PROPORTIONALITY**

Sucralfate oral suspension is available at the single strength of 1 g/5 ml.

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

This section is not applicable since no clinical studies have been conducted.

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2.5.2.4 INFLUENCE OF FOOD ON EXPOSURE

According to the SmPC of the Reference product Antepsin, sucralfate should be taken on an empty stomach, approximately one hour before meals and at bedtime, since sucralfate may bind with other foods which may cause blockage of the stomach and bowels.

2.5.2.5 INFLUENCE OF METHOD OF ADMINISTRATION

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

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

2.5.3.1 PHARMACOKINETICS

2.5.3.1.1 Absorption

Because of its poor solubility, a small amount of sucralfate is absorbed from the gastrointestinal tract (mostly as the intact sulphated disaccharide, which is then excreted in the urine) [142]. In 6 healthy male subjects, the total urinary excretion of radioactivity was 0.5 to 2.2 % over a 4-day period after a single 1 g dose of labelled drug (as reported by [REDACTED]). Maximum urinary excretion occurred during the first 4 hours after administration.

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 ¹⁴C-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 [144].

Aluminium absorption during sucralfate therapy is comparable to that during treatment with aluminium hydroxide [145-147]. 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 [147].

Although plasma levels of aluminium in normal subjects are generally believed not to rise during up to 12 months of sucralfate therapy [50, 51], in two studies substantial increases were found in normal subjects after 2 to 21 days of sucralfate (4 g/day) [148, 149]. Plasma aluminium levels do increase in a dose-dependent manner in sucralfate-treated patients undergoing dialysis [147], and aluminium intoxication has developed in at least four such patients during sucralfate therapy [147, 150, 151]. Statements that sucralfate may be "the phosphate-binding agent of choice" in patients with uraemia who have ulcers should be taken with some caution [145, 147, 152]. Like aluminium-containing antacids, sucralfate can cause severe hypophosphatemia. The problem of aluminium retention is likely to be negligible except perhaps in long-term users with renal insufficiency, especially those undergoing dialysis [145, 147, 150, 151].

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The study of [REDACTED] demonstrated significant aluminium absorption during the treatment of patients with 1 g sucralfate q.i.d. and has demonstrated that the significant elevation of urinary aluminium excretion persists for between 3 and 6 weeks after cessation of treatment [153].

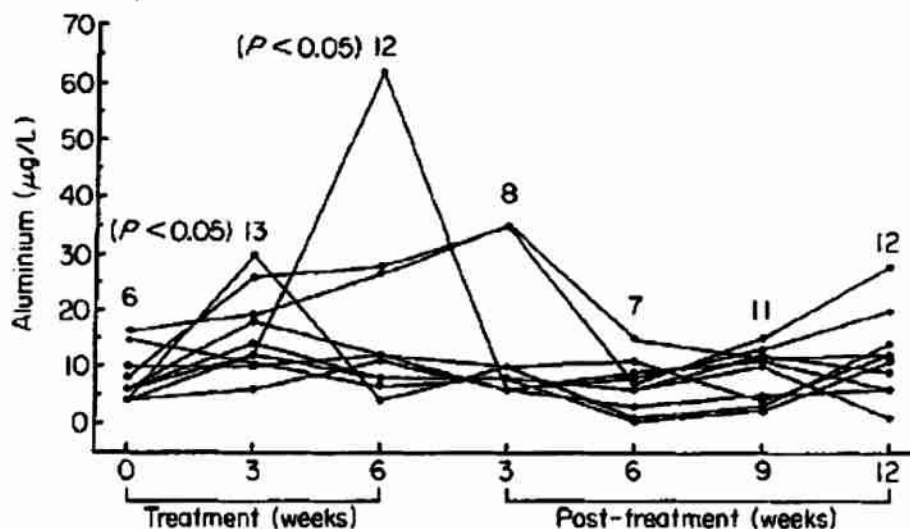


Figure 6 Plasma aluminium concentration before, during treatment with 1 g sucralfate q.i.d. for six weeks, and after treatment in 10 patients [153]

The 6-week course of treatment with 1 g sucralfate q.i.d. entails the oral ingestion of 35 g of aluminium. Assuming that each urine collection was representative of aluminium excretion during the preceding three weeks, it was calculated that the median increase of aluminium excretion during 6 weeks of treatment with sucralfate was approximately 2.3 mg and that further 0.6 mg was excreted in the 3 weeks after treatment. This is a minimum estimate of aluminium absorption, but it means that at least 0.01 % of orally administered aluminium taken as sucralfate is absorbed during treatment, an estimate similar to that obtained in previous studies.

2.5.3.1.2 Distribution

The true extent of distribution is unknown, but animal studies have demonstrated elevated amounts in hair, brain, and bone in dialysis patients [154]. Short-term aluminium loading studies show a correlation between serum aluminium concentration and aluminium load, but in long-term studies, no such correlation exists [155]. The large volume of distribution, at least in part, likely contributes to the long elimination half-life of aluminium observed in the study of [REDACTED]

Plasma protein binding of aluminium is concentration-dependent [157], and therefore it has been suggested that renal clearance may decrease as serum concentration increases. However, in a study of subjects with normal renal function [158], fractional excretion increased with increasing serum aluminium levels. This finding would support the concept that aluminium excretion by the kidney is more than just glomerular filtration.

2.5.3.1.3 Metabolism and Excretion

[REDACTED] reported that the elimination half-life of aluminium was 13.1 days after a 3-week course of therapy [156].

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2.5.3.1.4 Pharmacokinetics Related to Intrinsic Factors

2.5.3.1.4.1 Age, Sex, Race, Weight

Effects of age, sex, weight or racial effects on the pharmacokinetics of sucralfate have not been reported.

2.5.3.1.4.2 Renal Impairment

The product should only be used with caution in patients with renal dysfunction, due to the possibility of increased aluminium absorption [159]. Sucralfate is not recommended for use in individuals on dialysis. In patients with severe or chronic renal impairment, Antepsin should be used with extreme caution and only for short-term treatment. Small amounts of aluminium are absorbed through the gastrointestinal tract and aluminium may accumulate [159].

2.5.3.1.4.3 Hepatic Impairment

Effect of hepatic impairment on the pharmacokinetics of sucralfate has not been reported.

2.5.3.1.5 Pharmacokinetics Related to Extrinsic Factors

2.5.3.1.5.1 Smoking

Effects of cigarette smoking on the pharmacokinetics of sucralfate have not been reported.

2.5.3.1.5.2 Diet

This section is not applicable. Sucralfate should be taken on an empty stomach.

2.5.3.1.6 Pharmacokinetic Studies in Special Population

2.5.3.1.6.1 Paediatrics

Sucralfate is not recommended for use in children under 14 years of age.

2.5.3.1.6.2 Geriatrics

██████████ examined the effects of sucralfate on plasma and urine aluminum concentrations in the elderly. Subjects were 20 healthy volunteers over age 65 years, with no clinically significant comorbidities or recent use of aluminum-containing drugs or H₂-antagonists. Sucralfate 4 g/day in elderly subjects produced a significant increase in both plasma and urine aluminum concentrations, compared with ranitidine 300 mg/day. This increase most likely was secondary to gastrointestinal absorption of aluminum in the sucralfate formulation [160].

2.5.3.1.7 Pharmacokinetic Drug Interactions

When the following drugs are administered with sucralfate, the absorption and bioavailability of single doses are substantially reduced: ciprofloxacin [161-164], norfloxacin [165, 166], theophylline, tetracycline, aminophylline, phenytoin [167, 168], digoxin, and amitriptyline. The bioavailability of digoxin, tetracycline, and phenytoin was not reduced when they were given two hours before sucralfate. At present sucralfate should not be used if fluoroquinolone antibiotics are required [162].

2.5 Clinical overview

The effects of long-term administration of these drugs during sucralfate therapy have not been studied.

The ability of sucralfate to delay slightly the absorption of cimetidine and ranitidine, though of some pharmacokinetic interest [169-171] is not clinically important; interactions with other H₂ antagonists or omeprazole have not been studied. Some drugs whose bioavailability is not influenced substantially by administration in combination with sucralfate include acetaminophen, aspirin, diazepam, erythromycin, ethinyl oestradiol, ibuprofen, imipramine, indomethacin, ketoprofen, naproxen, prednisone, propranolol, quinidine, and warfarin. The effect of combined therapy with antacids has not been evaluated in humans; in animals, antacids given shortly (15 minutes) before sucralfate diminish its binding to gastric ulcers.

2.5.3.2 PHARMACODYNAMICS

2.5.3.2.1 Mechanism of Action

Sucralfate is the only extensively used clinical drug, apart from CBS, which gives both acute gastroprotection and acceleration of chronic ulcer healing without a substantial decrease in gastric acidity [172]. Its multiple mechanisms of action are presented in Table XV below.

Table XV Mechanism of action of sucralfate [173]

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

The normal, damaged and protected mucosa is presented in the following figure.

2.5 Clinical overview

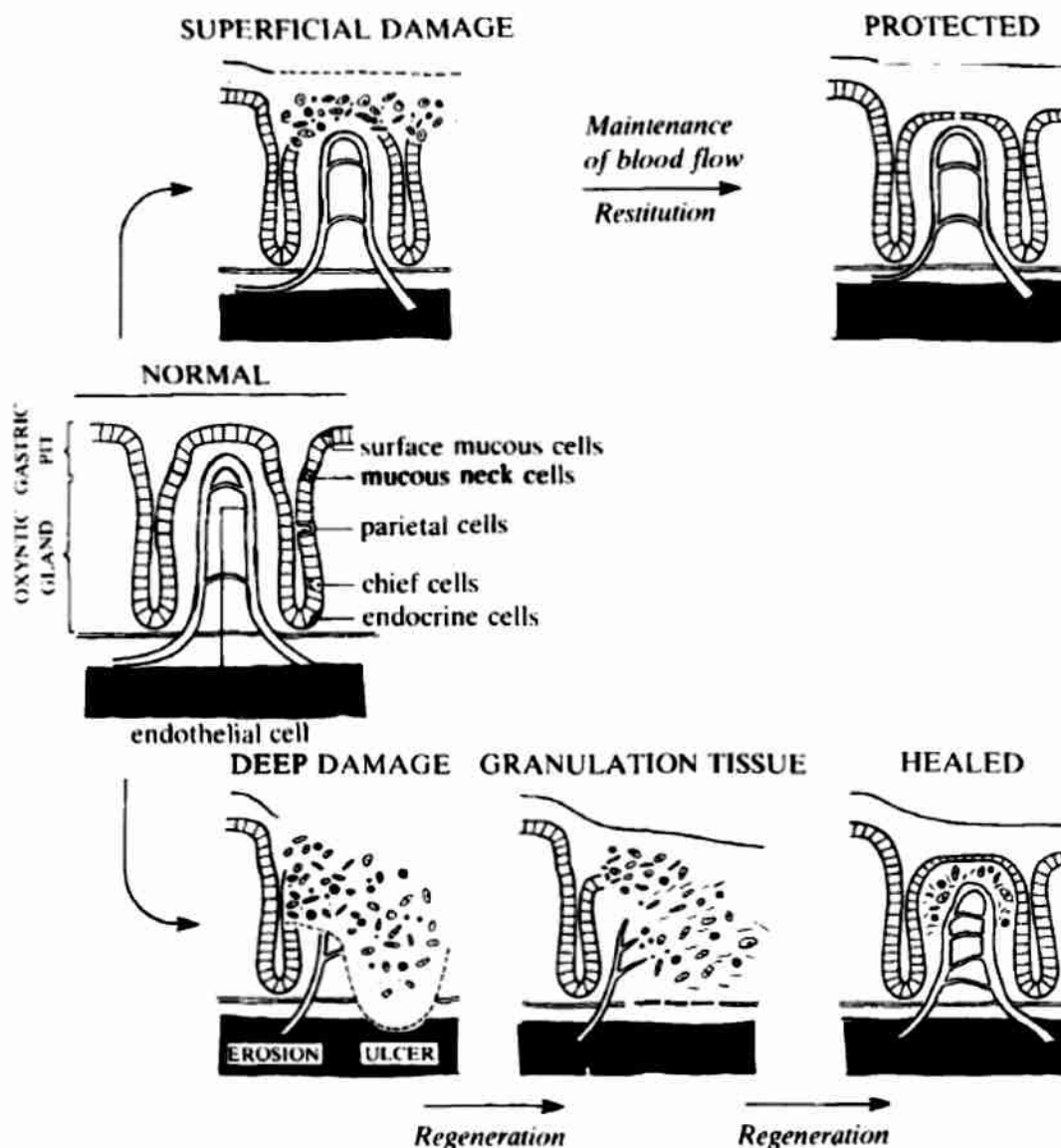


Figure 7 Normal, damaged, protected, and healed mucosa. Top: After pretreatment with a gastroprotective agent, such as sucralfate. Bottom: After deep erosion and ulceration, cell regeneration (multiplication) involving angiogenesis and fibroblasts [172]

Another clinically useful classification of the mechanisms of action of sucralfate is the analysis of its mechanisms of action as related to acute gastroprotection and long-term ulcer healing (Table XVI).

2.5 Clinical overview

Table XVI Mechanisms of action of sucralfate relevant to acute gastroprotection and chronic ulcer healing [172-174]

Actions of Sucralfate	Acute Gastroprotection	Chronic Ulcer Healing
↓ Pepsin and bile acids	+	++
↑ Bicarbonate and mucus	+	++
↑ Prostaglandin synthesis	+	?
↑ Epidermal growth factor binding	±	++
↑ Macrophage activity	?	+
Binding to endogenous sulfhydryl	++	+
Protection of vascular integrity	++	?
Protection of proliferative zone	++	-
Stimulation of epithelial restitution	++	+
Stimulation of cell proliferation	-	++

Preferential binding of sucralfate to ulcer sites was demonstrated in a study of patients who underwent gastric resection. The concentrations of sucralfate in ulcer craters were 4-30 times higher than the concentrations in tissue specimens from the normal gastric mucosa in the same patients [175]. The effects of sucralfate on pepsin activity have been also demonstrated in patients with peptic ulcer disease (as described in [144]).

As demonstrated by Szabo (1991), of the multiple actions of sucralfate, not all are equally relevant. In fact, certain actions of the drug contribute to healing of acute ulcers or to ulcer prevention, whereas other actions are more important in accelerating the healing of gastric and duodenal ulcers. The action of sucralfate can now be defined by the “1 × 1 × 1” mechanism of action—that is, one action of sucralfate is important for acute prevention, one is relevant to both acute and chronic protection, and one is important for chronic ulcer healing. Maintenance of mucosal vascular integrity and of blood flow, which ensures rapid epithelial restitution to repair superficial defects, are the most important acute actions of sucralfate. On the other hand, increased bicarbonate and mucus secretion seem to be relevant in both acute and chronic protection of the gastroduodenal mucosa. Finally, the enhanced binding by sucralfate of fibroblast growth factor and epidermal growth factor stimulates angiogenesis, granulation tissue, and epithelization for ulcer healing [172].

2.5.3.2.2 Primary Pharmacodynamics

2.5.3.2.2.1 *Adsorption of bile acids and pepsin*

Bile acid binding activity of sucralfate is pH dependent [176]. At a high pH, the binding effect of bile acids is decreased. Sucralfate not only adsorbs pepsin but also reduces its activity.

2.5.3.2.2.2 *Cytoprotective activity of sucralfate*

Experiments have shown that sucralfate interacts with the mucosa and prevents injury with an increased synthesis and release of prostaglandins by the gastric mucosa [176, 177]. Medicine which blocks endogenous synthesis of prostaglandins decreases the protective activity of sucralfate substantially. That sucralfate is a mucosal protective agent due to the release of mucosal prostaglandin has been confirmed in studies with humans [175, 176, 178]. However, it has been demonstrated that the cytoprotective actions of sucralfate can be quite prostaglandin-independent, as in mucus and bicarbonate secretion, and mucosal blood flow [179]. Sucralfate also prevents gastric mucosal damage

2.5 Clinical overview

caused by acholic acid and aspirin. The protective effect of sucralfate against aspirin does not seem to be entirely caused by an increased release of mucosal prostaglandins since the release of prostaglandins is suppressed under this condition. The effects of sucralfate on mucosal prostaglandins in humans is controversial.

2.5.3.2.2.3 *Ulcer coating effect*

Sucralfate becomes a viscous substance where it is exposed to gastric acid. It forms an adherent and protective chemical complex with proteins at the ulcer site which acts as an effective barrier against the actions of acid, pepsin and bile salt. Studies in patients with duodenal or gastric ulcer have shown that sucralfate is selectively bound to the ulcer site [175, 180]. Sucralfate stimulates mucous secretion and bicarbonate secretion by the gastric mucosa [176, 181]. It has been shown in humans, but it is not clear whether the stimulation of bicarbonate secretion is totally or only partly prostaglandin dependent.

2.5.3.2.2.4 *Effects on vascular integrity*

The mucosal vascularization is very important in maintaining oxygenation and transporting nutrients to the various layers of the mucosa. Pretreatment with sucralfate in rats reduces vascular injury induced by alcohol [181]. The preservation of gastric micro-vascularization is important for the energy-dependent restitution developing surface epithelial damage. Furthermore, sucralfate has actually been shown to increase gastric mucosal blood flow [182].

The most important events of sucralfate in the acute gastric protection are the protection of the vascular integrity and proliferative zone assuring an effective and rapid epithelial restitution after an acute injury of the mucosa.

The effect of sucralfate or acute gastroprotection on bicarbonate and mucus secretion is unclear. In contrast in chronic peptic ulcers the healing effect of sucralfate is accelerated by the increased secretion of bicarbonate and mucus, the natural defence factors against acid and pepsin [174]. Studies have indicated that sucralfate increases the binding to the gastric mucosa of epidermal growth factor and thereby increases the local concentration of this factor within the ulcer [183]. Epidermal growth factor is known to stimulate cellular growth and cell proliferation whereby it could facilitate the healing of a damaged mucosa. An effect of sucralfate, which may be important for its ability to prevent repeated treatment, is its trophic effect on the gastric mucosa including thickening of the surface epithelial zone up to more than 80 % together with an increase in the number of cells.

2.5.3.2.2.5 *Effect of Sucralfate on Campylobacter pylori in Ulcer-Associated Antral Gastritis*

It has been shown that sucralfate improves the activity of gastritis more frequently than cimetidine. The density of *C. pylori* has been shown to decrease significantly in sucralfate treated patients compared with patients treated with cimetidine. Thus, sucralfate improves duodenal ulcer-associated antral gastritis and decreases the density of *C. pylori* [184]. It has been postulated but not proven that CBS improves gastritis, promotes ulcer healing and delays ulcer recurrence because of its bactericidal effect on *C. pylori* [185, 186]. In one study, CBS has been shown to be effective in the treatment of gastritis produced by *C. pylori*. Of the 40 patients treated with CBS for 8 weeks half were found to be free of the organisms. Amoxicillin was found to produce a similar histological improvement.

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2.5.3.2.3 Secondary Pharmacodynamics

EGF stimulates mostly epithelial cell proliferation with very little effect, if any, on angiogenesis and other components of granulation tissue such as fibroblasts and monocytes. On the other hand, FGF is the most potent endothelial mitogen [187] that also stimulates granulation tissue formation and epithelization. Previous studies demonstrated an enhanced binding of EGF to sucralfate-treated ulcers [183]. Other studies showed strong and preferential binding of FGF to sucralfate and SOS. These in vitro studies also demonstrated that the FGF binding to sucralfate and SOS was even more potent than that of heparin, and this strong binding was acid sensitive. The relevance of these in vitro binding studies of sucralfate to FGF might correlate with in vivo animal experiments with the subcutaneously implanted sponge assay, in which both sucralfate and its active component SOS stimulated angiogenesis, whereas it was mostly sucralfate and not SOS which enhanced the area of granulation tissue in the subcutaneous sponge in rats [188]. It has been proposed [188] that one of the most relevant actions of sucralfate in its acid-independent stimulation of chronic ulcer healing is the enhanced binding of FGF, EGF, and possibly other growth factors that stimulate granulation tissue formation, angiogenesis, and epithelization. These actions would explain the powerful ulcer healing actions of sucralfate without decreasing gastric acid concentration in the stomach and the duodenum.

2.5.3.2.4 PK/PD Relationships

PK/PD relationship studies were not identified for sucralfate.

2.5.3.2.5 Genetic Differences

Effects of patients' genetic differences on the pharmacodynamics of sucralfate have not been published.

2.5.3.2.6 Pharmacodynamic Drug Interactions

Pharmacodynamic drug interactions have not been reported for sucralfate. The pharmacokinetic drug interactions are presented in section 2.5.3.1.7.

2.5.4 OVERVIEW OF EFFICACY

2.5.4.1 DUODENAL ULCER

In the five randomized, double-blind, and interpretable trials [34, 142] a total of 213 patients treated with sucralfate (1 g four times a day) were compared with 217 placebo-treated patients. The average rates of healing, weighted for sample size, in the patients treated with sucralfate were 34.7 % (after 2 weeks in two trials), 77 % (after 4 weeks in three trials), 60 % (after 6 weeks in one trial), 82 % (after 8 weeks in one trial), and 77 % (after 12 weeks in one trial) [34] (Table XVII). In all studies, sucralfate was significantly better than placebo. The rates of healing in the placebo-treated patients also varied considerably, with the highest rates in the two U.S. studies (58 and 64 % healing after four weeks) and the lowest in China (25 % after four weeks) and South Africa (24 % after six weeks).

2.5 Clinical overview

Table XVII Randomized, double-blind trials of sucralfate in patients with duodenal ulcers [142]

Study	N	Drug	Dose	Other drugs	Percentage of patients healed				
					2 weeks	4 weeks	6 weeks	8 weeks	12 weeks
1	17	Sucralfate	1 g qid	NR	-	-	-	82	-
	18	Placebo	-	NR	-	-	-	39	-
2	24	Sucralfate	1 g qid	Antacid	33	92	-	-	-
	31	Placebo	-	Antacid	13	58	-	-	-
3	109	Sucralfate	1 g qid	Antacid	35	75	-	-	-
	107	Placebo	-	Antacid	25	64	-	-	-
4	30	Sucralfate	1 g qid	None	-	-	60	-	77
	29	Placebo	-	None	-	-	24	-	44
5	33	Sucralfate	1 g qid	None	-	73	-	-	-
	32	Placebo	-	None	-	25	-	-	-
6	177	Sucralfate	1 g qid	Antacid	-	71	-	86	-
	194	Cimetidine	400 mg bid	Antacid	-	77	-	92	-
7	30	Sucralfate	1 g qid	Antacid	-	80	-	90	-
	29	Cimetidine	300 mg qid	Antacid	-	76	-	86	-
8	35	Sucralfate	1 g qid	NR	-	85	-	91	-
	35	Cimetidine	200mg qid	NR	-	84	-	90	-
9	44	Sucralfate	1 g qid	NR	-	73	89	-	-
	37	Cimetidine	NR	NR	-	76	92	-	-
10	18	Sucralfate	1 g qid	Antacid	-	72	-	-	-
	19	Cimetidine	1 g qd	Antacid	-	74	-	-	-
11	20	Sucralfate	1 g qid	None	-	65	-	85	-
	20	Cimetidine	300 mg qid	None	-	75	-	85	-

There have been six randomized, double-blind, controlled trials comparing sucralfate and cimetidine [28, 35-37] (Table XVII). In these, the rate of healing in a total of 324 patients treated with sucralfate (1 g four times a day) was compared with that in 334 patients treated with cimetidine (800 to 1200 mg/day). The average healing rates in 278 patients treated with sucralfate were 73 % (after 4 weeks in six trials) and 87 % (after 8 weeks in four trials), as compared with 77 % and 91 %, respectively, in 262 cimetidine-treated patients. In 10 additional open or single-blind studies of sucralfate (1 g four times a day), 1 in comparison with ranitidine [38] and 9 in comparison with cimetidine [39-43], the healing rates were similar.

Sucralfate and ranitidine were compared in the treatment of duodenal ulcer in this multi-centre, randomized, double-blind study. A total of 165 patients with endoscopically proven duodenal ulceration were included in the trial and randomized to treatment with sucralfate, 2 g b.i.d. (morning and evening with an empty stomach), or ranitidine, 150 mg twice daily. All patients were endoscopically examined after 4 and, if unhealed, 8 weeks. At 8 weeks cumulative healing rates were 89 % (74 of 83) and 84.8 % (67 of 79), respectively. When smokers were considered separately, healing rates at 4 weeks were 69.2 % (36 of 52) for sucralfate and 53.3 % (24 of 45) for ranitidine. At 8 weeks cumulative healing rates were 92.3 % (48 of 52) and 77.7 % (35 of 45), respectively ($p < 0.05$) [44].

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██████████ compared two different dosing schemes of sucralfate for the treatment of duodenal ulcer. Seventy-seven patients with endoscopically verified duodenal ulcers were randomized to treatment with either 2 g sucralfate daily at bedtime or 1 g sucralfate q.d.s. in a controlled double-blind comparative study. After a 4-week treatment period, the healing rate was 68 % for the former and 69 % for the latter treatment. No difference was observed in symptoms between the two groups, either at entrance or at the end of the 4-week treatment period [29].

Similarly, ██████████ evaluated a twice-daily dosing with sucralfate by two multi-centre trials, trial 1 (eight weeks) and trial 2 (four weeks). Both trials demonstrated significantly better ulcer healing at study completion for the 2-g twice daily (B.I.D.) regimen compared with placebo. Both trials were double-blind, randomized, and placebo-controlled, with parallel groups. Patients received two doses daily consisting of sucralfate 2 g B.I.D., placebo/sucralfate 2 g at bedtime (H.S.), or placebo/placebo. Ulcer healing was assessed by scheduled endoscopy and symptom assessment. Healing was defined as complete absence of erosion or ulceration. Trial 1 evaluations were conducted at four and eight weeks, trial 2 evaluations at two and four weeks. Treatment groups were comparable with regard to number of patients, age, sex, smoking status, ulcer size, and presence/absence of baseline symptoms. Sucralfate 2 g B.I.D. was significantly better than H.S. or placebo dosing at the completion of each trial. H.S. dosing was better than placebo only at the four-week analysis of trial 1. At Week 4 of trial 1, 14 of 54 patients (26 %) were healed with the B.I.D. sucralfate regimen, whereas at Week 8, 41 of 54 (76 %) were healed ($p < 0.001$). For the placebo/sucralfate H.S. group, 17 of 57 patients (30 %) were healed at Week 4 ($p < 0.05$) and 32 of 56 patients (57 %) were healed at Week 8. For the placebo group, six of 52 (12 %) and 20 of 51 patients (39 %) were healed at Weeks 4 and 8, respectively. In trial 2, the B.I.D. group had a 21 % healing rate at Week 2 (13 of 61 patients) and 62 % were healed at Week 4 (38 of 61 patients; $p < 0.05$). The H.S. group had an 8 % healing rate (five of 66 patients) at Week 2 and 50 % (33 of 66 patients) at Week 4. For the placebo group, 10 of 62 patients (16 %) and 26 of 62 patients (42 %) were healed at Weeks 2 and 4, respectively. Trial 1 demonstrated significant symptom improvement for active treatment groups at both four and eight weeks, whereas no differences were found in trial 2 [45].

Smoking and Ulcer Healing

██████████ have claimed that duodenal-ulcer healing was delayed in smokers treated with H_2 -antagonist agents but not sucralfate [39]. This study was not stratified according to smoking status or ulcer size (ulcers are known to be larger in smokers), was not double blind or placebo-controlled, and did not prohibit or record the consumption of alcohol, analgesics, or traditional Chinese ulcer remedies, and thus it has been subjected to serious criticism [189]. Some studies lend support to Lam's claim [190], but others do not [28, 46-48]. In a randomized, double-blind trial comparing sucralfate and placebo in 293 patients in Canada, patients who smoked had significantly lower healing rates after four and eight weeks than those who did not, regardless of treatment group [47]. Furthermore, a meta-analysis of the outcome of therapy in 4451 patients from 30 trials (involving 64 treatment groups and 15 placebo groups) that met predetermined criteria for inclusion did not show any advantage for sucralfate or reveal impaired healing in patients taking any other drug, once the rates were corrected for the effect of smoking on healing in the placebo-treated patients [191].

Relapse Rates after Healing in Patients Treated with Sucralfate

A final issue is whether patients with duodenal ulcers that healed with sucralfate have lower relapse rates than patients treated with H_2 -antagonist drugs [190]. Although retrospective analysis and

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inappropriate pooling of data from a number of studies not designed to assess the issue [190] support a possible advantage for sucralfate, no valid conclusion can be drawn from this analysis.

In the study of [REDACTED], one hundred and fourteen duodenal ulcer patients were randomized to the treatment over a 12-month period. Fifty-seven of them received triple therapy consisting of 1 g sucralfate q.d.s. for 28 days, 300 mg metronidazole q.d.s. for 14 days and 250 mg clarithromycin q.d.s. for 14 days. Another 57 received 20 mg omeprazole q.d.s. for 12 months. An upper endoscopy was performed before treatment, at 6 weeks, and 2, 6 and 12 months after the first endoscopy. The ulcer healing rate was 90.2 % (95 % CI: 79-97 %) in the omeprazole group at 6 weeks as compared to 83.3 % (95 % CI: 70-93 %) in the triple therapy group ($p=0.38$). There was a higher success rate of pain control in the omeprazole group. Side-effects were more frequently reported, and compliance was poorer in the triple therapy group during the first 4 weeks. During follow-up, more relapses were seen in the omeprazole group (9.8 %, 95 % CI: 3-21 %) than the triple therapy group (4.2 %, 95 % CI: 1-13 %) at 1 year ($p=0.44$). All relapses were due to the persistence of *H. pylori* infection. At the 1-year follow-up, none of the patients who were *H. pylori* negative had an endoscopic relapse compared to 7 out of 56 patients who remained *H. pylori* positive (12.5 %, 95 % CI: 5-24 %, $p=0.018$). After a mean follow-up of 4.07 years, none of those who remained *H. pylori* negative had an ulcer relapse while the 11 out of 41 who remained *H. pylori* positive had an ulcer relapse (26.8 %, 95 % CI 14-43, $p=0.0005$) [49].

The cumulative recurrence rates of duodenal rates are presented in the figures below:

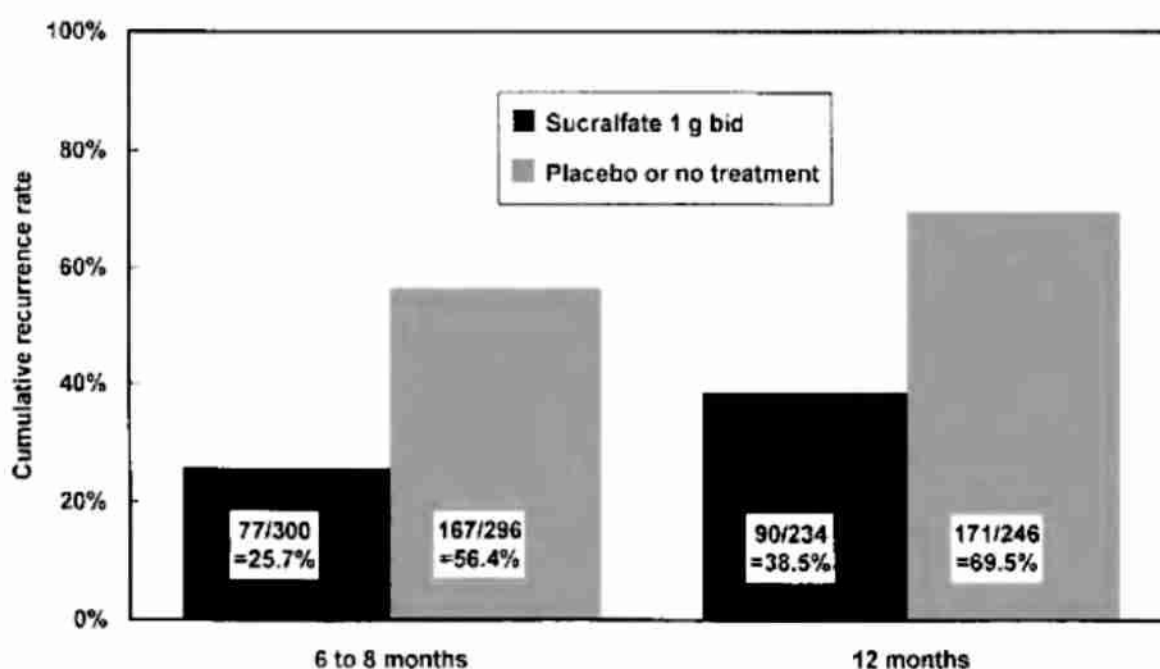


Figure 8 Cumulative recurrence rates of duodenal ulcers during long-term treatment with sucralfate 1 g bid or placebo [192]

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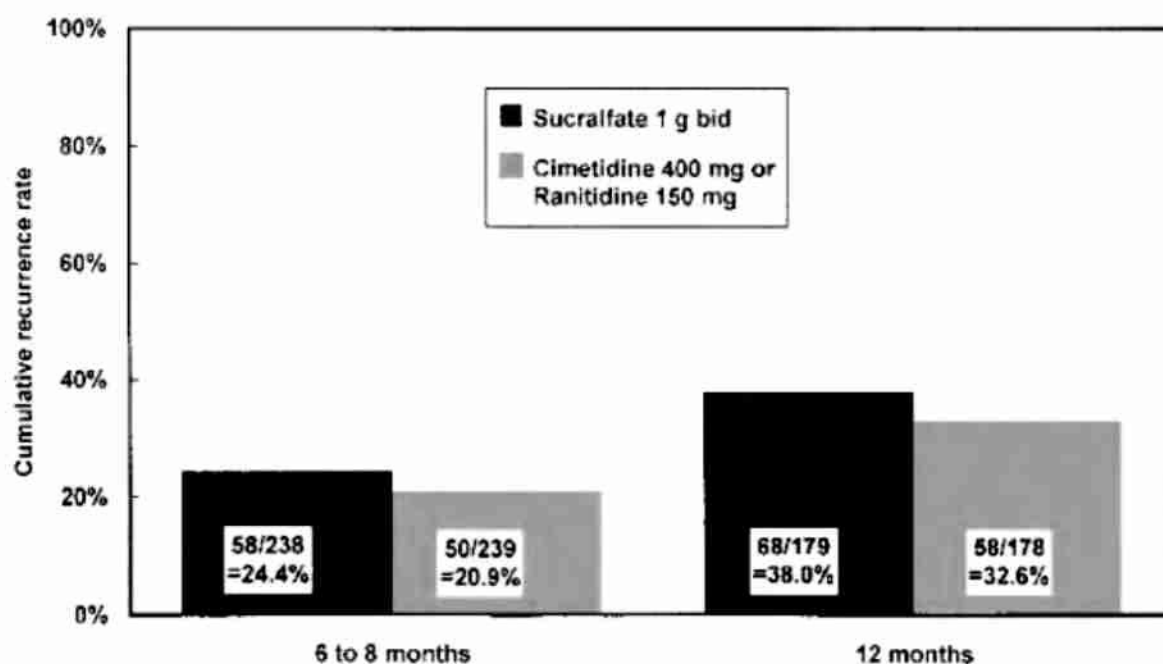


Figure 9 Cumulative recurrence rates of duodenal ulcers during long-term treatment with sucralfate 1 g bid or H₂-receptor antagonist (cimetidine 400 mg or ranitidine 150 mg at bedtime [192])

2.5.4.2 MAINTENANCE THERAPY FOR DUODENAL ULCER

The efficacy of sucralfate (2 g/day) in preventing the recurrence of duodenal ulcers has recently been reviewed [193]. In five randomized, placebo-controlled, double-blind 12-month trials [50-53], the weighted average 12-month recurrence rates as assessed by endoscopy were 38 % in 150 patients treated with sucralfate and 70 % in patients given placebo. In one of those studies [52], in which the 12-month recurrence rate was 27 % in patients treated with sucralfate as compared with 81 % in patients given placebo, "erosions or superficial ulcers" were not considered recurrences. In a recent randomized, double-blind four-month study of 122 patients [54], endoscopy was performed monthly and whenever symptoms recurred. By the fourth month, ulcers had recurred in 55 % of the placebo treated and 36 % of the sucralfate-treated patients, as shown by cumulative point-prevalence analysis, and in 63 and 42 %, respectively, on the basis of life-table estimates [54].

One moderate-sized study in Japan compared the rate of ulcer recurrence in patients taking sucralfate (2 g/day) with that in patients taking cimetidine (400 mg/day) or a combination of both drugs. After one year the recurrence rates were similar: 60 % in patients taking cimetidine, 58 % in patients taking sucralfate, and 52 % in patients taking both drugs. In four small single-blind studies [53, 55-57] of maintenance therapy with sucralfate (2 g/day) or H₂-antagonist agents, cimetidine (400 mg at bedtime; 79 patients) and ranitidine (150 mg at bedtime; 15 patients), no clinically important or statistically significant differences emerged.

The double-blind, randomized, placebo-controlled, parallel groups, multi-centre clinical study with 254 patients of [REDACTED], compared the efficacy of sucralfate to placebo for the prevention of duodenal ulcer recurrence. Sucralfate or placebo were dosed as a 1-g tablet twice a day for 4

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months, or until ulcer recurrence. Endoscopic examinations once a month and when symptoms developed determined the presence or absence of duodenal ulcers. Sucralfate was significantly superior to placebo in reducing ulcer prevalence by all analyses. Significance ($p < 0.05$) was found at months 3 and 4 for all analyses. All months were significant in the traditional analysis, months 2-4 in point-prevalence analysis, and months 3-4 in the maximal ulcer prevalence analysis. Sucralfate was shown to be effective for the prevention of duodenal ulcer recurrence by a true reduction in new ulcer development [58].

performed a randomized controlled trial to compare the efficacy of seven forms of maintenance treatment of duodenal ulcer, including a mealtime regimen of antacids. 785 patients with healed duodenal ulcer were randomized to receive: (1) no treatment; (2) mealtime antacids with an acid-neutralizing capacity of 80 mmol/day; (3) an antidepressant, trimipramine 25 mg; (4) an anticholinergic, pirenzepine 50 mg; (5) cimetidine 200 mg; (6) cimetidine 400 mg; (7) ranitidine 150 mg; or (8) sucralfate 1 g twice a day. The cumulative percentages of patients with relapse of ulcers at 12 months by life-table analysis were 61 % with no treatment, 38 % with mealtime antacids, 60 % with trimipramine, 52 % with pirenzepine, 46 % with cimetidine 200 mg, 44 % with cimetidine 400 mg, 30 % with ranitidine 150 mg, and 40 % with sucralfate. Cimetidine 400 mg, antacids, ranitidine 150 mg, and sucralfate were significantly better than no treatment and the other forms of treatment [59].

Acid secretory responses and PCS have been studied in 21 duodenal ulcer patients before and after successful treatment with omeprazole ($n=7$), sucralfate ($n=7$), or Maalox ($n=7$). The second study was carried out 3 days after documented healing and withdrawal of treatment in the sucralfate- and Maalox-treated groups and 14 days after documented healing and withdrawal of treatment in the omeprazole-treated patients. Acid output (mmol/hour) was measured as basal secretion, and in response to 0.1 $\mu\text{g/kg/hour}$ pentagastrin (low-dose) and 6.0 $\mu\text{g/kg/hour}$ pentagastrin (high-dose) stimulation. PCS was calculated as the ratio of low dose:high dose acid output (expressed as a percentage). Ulcer healing with sucralfate resulted in significant ($p < 0.05$) decreases in low-dose acid output from 36.4 % (13.2-51.0) (median [range]) to 8.4 % (3.2-45.4) mmol/hour and PCS from 69.1 % (44.9-91.4) to 22.0 % (16.0-85.61), whereas no significant decreases in any of the measured parameters were noted following ulcer healing with Maalox. Ulcer healing with omeprazole resulted in significant ($p < 0.05$) decreases in basal acid output from 6.3 (1.5-22.9) (median [range]) to 2.2 (0-6.9) mmol/hour, and low-dose acid output from 31.0 (6.0-58.0) to 23.0 (1.4-44.8) mmol/hour [60].

In the study of a total of 46 patients with duodenal ulcer were randomly assigned to treatment with cimetidine 200 mg three times daily and 400 mg at night or sucralfate 1 g four times daily followed by one year of maintenance treatment with cimetidine 400 mg at night or sucralfate 1 g twice daily, respectively, in those patients with healed ulcers. The endoscopic healing rates and relapse rates during the maintenance period were similar, four relapses occurring in each group. All four relapses in the sucralfate group occurred at 12 months and only two were symptomatic. All the cimetidine relapses were symptomatic, two occurring at six months, one at nine months, and one at 12 months. Following the one-year maintenance period, 13 cimetidine patients and 11 sucralfate patients were followed up for 36 months. During the first two years, nine of 13 (69 %) cimetidine-treated and two of 11 (18 %) sucralfate-treated patients had relapses. During the third year, three more sucralfate-treated patients and one more cimetidine-treated patient had relapses, making a total of 10 of 13 (77 %) and five of 11 (45 %) in the cimetidine and sucralfate groups, respectively. Duodenal biopsy specimens obtained before and after healing and after one year of maintenance were examined by light and electron microscopy.

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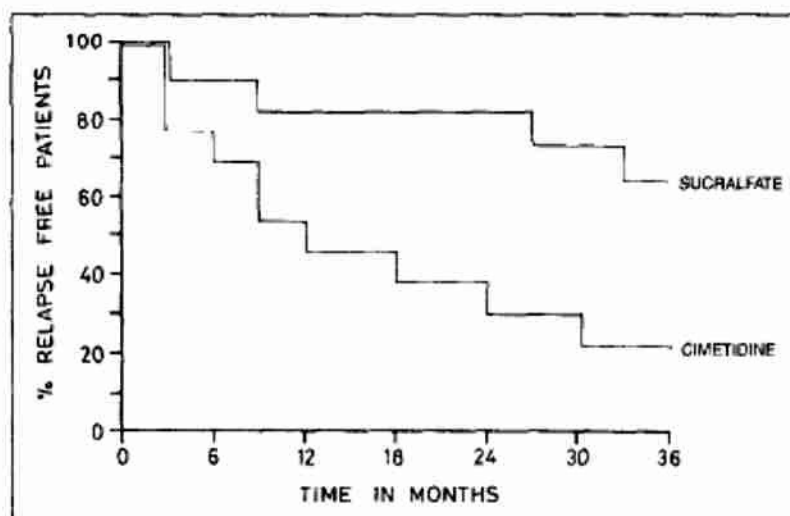


Figure 10 Relapse-free patients during the 3-year period following one year of maintenance of duodenal ulcer patients with either sucralfate or cimetidine [61]

The sucralfate group showed greater improvement after one year of maintenance therapy than did the cimetidine group, although the appearances in either group were not predictive of subsequent relapse [61].

Healing and relapse of acute duodenal ulcer were investigated in an endoscopically controlled multi-center study using a double-blind design. Patients with acute uncomplicated duodenal ulcer were randomly assigned to treatment with sucralfate (1 g four times per day) or ranitidine (150 mg twice per day) for four to eight weeks. After healing, all anti-ulcer treatment was discontinued except for low-dose antacids needed for occasional upper abdominal pain, and the patients were observed for up to one year. Endoscopy was repeated after one year or at any time earlier if symptoms suggested ulcer relapse. Of the 83 patients who entered the study, 75 (sucralfate 40, ranitidine 35) underwent endoscopy after four weeks and could be fully evaluated. Healing rates after four and eight weeks were similar in the two groups (four- and eight-week healing rates after sucralfate and ranitidine: 78 and 74 %, and 95 and 94 %, respectively). Fifty-three patients with healed ulcers (sucralfate 29, ranitidine 24) were observed for up to one year. Duodenal ulcers occurred somewhat later after sucralfate than after ranitidine treatment, but life table analysis showed no significant difference [62].

2.5.4.3 GASTRIC ULCER

Two placebo-controlled trials have assessed the efficacy of treatment with sucralfate (4 g/day) for eight or more weeks in patients with gastric ulcers [63]. The rates of healing were 60 % for sucralfate and 42 % for placebo ($p < 0.05$) after eight weeks in one study. In the second study, the benefit varied with the type of ulcer; sucralfate was no better than placebo in patients with gastric ulcers associated with duodenal ulcers [63]. However, ulcers of the gastric corpus healed in 80 and 90 % of the sucralfate-treated patients after 8 and 12 weeks, respectively, as compared with 40 and 52 % of the patients given placebo after the corresponding intervals ($p < 0.001$); prepyloric ulcers also healed well with sucralfate [63].

The healing of gastric ulcers in patients treated with sucralfate (4 g/day) or cimetidine (800 mg/day) has been compared in four trials [30, 64]. The average healing rates (weighted for sample size) at 4, 8,

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and 12 weeks, respectively, were 57, 88, and 96 % for sucralfate and 65, 88, and 94 % for cimetidine. Four additional single-blind or non-randomized studies showed similar healing rates [41, 46]. Two studies comparing sucralfate and ranitidine [65, 66], showed no differences between the two treatments. In one study sucralfate was superior to low-dose antacids after four and eight weeks of therapy.

In a double-blind, randomized study, [REDACTED] compared the healing of gastric ulcer during a twice-daily regimen of 2 g sucralfate or sucralfate 1 g q.i.d. Patients receiving the former therapy received the tablets one-half hour before breakfast and at bedtime. Patients receiving sucralfate 1 g q.i.d. received their therapy 30 minutes before breakfast, lunch, and supper, and at bedtime. The study included 52 patients with endoscopically proven gastric ulcer; 41 patients completed the study. Healing was endoscopically assessed at 8 weeks and 12 weeks. After 8 and 12 weeks the healing rate for sucralfate 2 g b.i.d. was 67 % and 92 %, respectively; the healing rate of sucralfate 1 g q.i.d. was 59 % and 71 %, respectively. No statistically significant difference was found between the two regimens. These results suggested that 2 g sucralfate twice daily is as effective in the healing of gastric ulcer as 1 g sucralfate q.i.d [67].

[REDACTED] performed a randomized, single-blind study in Japan to investigate the efficacy and safety of two dosage regimens of sucralfate granules, 2 g, twice daily (b.i.d. group, n=30) and 1 g, 4 times daily (q.i.d. group, n=27), on ulcer healing in 57 patients with endoscopically proven gastric ulcer. Endoscopy was performed after 4 weeks and, if complete healing was not achieved, again after an additional 4 weeks. Healing rates at 4 and 8 weeks were 50 % and 94 % in the b.i.d. group and 35 % and 68 % in the q.i.d. group. There was no significant difference in healing rates between the groups. These results suggest that the 2 g b.i.d. dose of sucralfate in granule form is at least as effective as the conventional dose of 1 g q.i.d. in the treatment of active gastric ulcers and could lead to better patient compliance [68].

The GISU group reported the results of the second year of a scheduled 3-year follow-up study. The 24-month follow-up was completed by 142 patients who were continuously either treated with the drug randomly assigned at the beginning of the study or left untreated (i.e. 32 patients took 150 mg ranitidine at bedtime, 29 took 1 g sucralfate twice daily and 81 were left untreated, 23 of whom came from the ranitidine group, 19 from the sucralfate group and 39 from the untreated group). Seven patients dropped out and 26 subjects relapsed (5 under ranitidine, 4 under sucralfate and 17 untreated cases). Ranitidine versus previous ranitidine, sucralfate versus previous sucralfate and each one versus no treatment showed comparable relapse rates. Both ranitidine 150 mg and sucralfate 2 g proved effective in reducing GU relapse as compared with no treatment [69].

Sucralfate and ranitidine were compared in the treatment of GU in the multi-centre randomized double-blind study of [REDACTED]. Sixty-four patients with endoscopically diagnosed GU initially included in the trial were randomly assigned to treatment with sucralfate, 2 g b.i.d. (morning and evening on an empty stomach), or ranitidine, 150 mg b.i.d. At 4 weeks, 54.2 % (13 of 24) of the sucralfate group had a healed ulcer, in comparison to 45.2 % (14 of 31) of the ranitidine group (NS). At 8 weeks, cumulative healing rates were 87.5 % (21 of 24) and 84 % (26 of 31), respectively (NS). No differences were found in the healing effects of the drugs on smokers and nonsmokers or in side effects [70].

Combining the results of the two studies reporting on the efficacy of sucralfate in prepyloric and corpus ulcers shows that the response curves of these two types of ulcers completely overlap (Figure 11). This further supports that the two types of ulcers are closely related pathogenetically.

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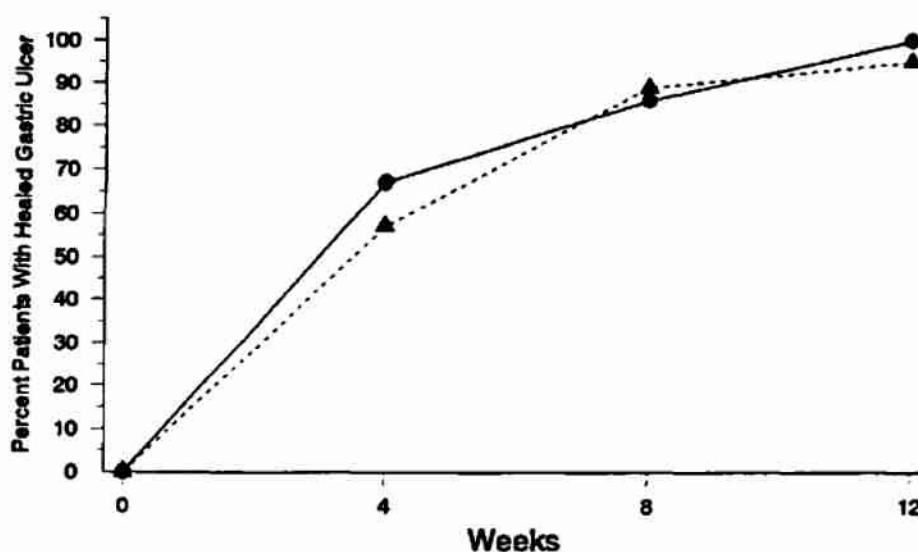


Figure 11 The healing curves of prepyloric (—●—, n=84) and corpus ulcers (---▲---, n=108) treated by sucralfate completely overlap [194]

2.5.4.4 PREVENTION OF RECURRENCES OF GASTRIC ULCER

Of seven studies of the efficacy of sucralfate in preventing a recurrence of gastric ulcers, four indicated a benefit of the drug [65, 71, 72, 195]. In a small but well executed randomized, double-blind, placebo-controlled 6-month study in South Africa, 122 the relapse rate was 16 % in the patients treated with sucralfate (1 g in the morning plus 2 g at night), as compared with 70 % in those given placebo ($p<0.001$); most relapses were symptomatic, since the only endoscopy was performed at 24 weeks. In 127 patients treated for 12 months with sucralfate (2 g/day), cimetidine (400 mg at bedtime), or both who underwent endoscopy every 3 months, the endoscopically determined relapse rates after 12 months were 20 % for sucralfate, 27 % for both drugs, and 55 % for cimetidine; the rates for the first two treatments were significantly different ($p<0.01$) from the rate for cimetidine alone, but not from each other. A comparison of sucralfate (1 g twice a day) and ranitidine (150 mg at bedtime) in groups of 18 subjects each, with endoscopy carried out every 6 months and whenever symptoms recurred [65], revealed relapse rates after 12 months of 44 % for sucralfate and 50 % for ranitidine. Finally, in a large 12-month study, sucralfate (1 g three times a day in 175 subjects) was compared with ranitidine (150 mg at bedtime in 171 subjects). The recurrence rates for ranitidine after 9 and 12 months (18 % and 21 %, respectively) were significantly lower than for sucralfate (30 % and 30 %, $p<0.05$) [72].

The study of [redacted] compared healing rates, relief of symptoms, frequency of adverse events, and proportion of patients in remission after one year follow up in 104 patients with active prepyloric ulcer during treatment with 40 mg omeprazole once daily or 2 g sucralfate twice daily, using a randomised double blind controlled trial. Healing rates after two, four, and six weeks were (omeprazole/sucralfate) 49 %/23 %; 83 %/59 %; 90 %/70 %, respectively. After two weeks, omeprazole was more efficient than sucralfate in relief of daytime and nocturnal epigastric pain, nausea, and heartburn. The proportion of patients in remission after one year follow up was significantly higher in the omeprazole group ($p<0.01$). Of the healed patients, ulcers recurred in 36 % in the omeprazole group and in 46 % in the sucralfate group. It is concluded that the ulcer healing rate was higher and

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symptom relief was more pronounced in the omeprazole group compared with the sucralfate group, and that more patients were still in remission after a one year follow up period [31].

2.5.4.5 GASTROINTESTINAL BLEEDING

2.5.4.5.1 Peptic Ulcer

In most patients with bleeding peptic ulcers, the bleeding stops spontaneously, and the patients do not have further episodes of bleeding; no form of pharmacologic therapy has altered these short-term outcomes [196]. In long-term maintenance studies, only ranitidine has been reported to reduce the recurrence of bleeding over a three-year period of follow-up [197].

During the 2-year period of the study of [REDACTED] 165 patients with one or more upper gastrointestinal haemorrhage risk factors were randomized into one of four groups. Patients received no treatment in the control group. The antacid group received almagate 0.25 to 0.5 ml/kg every 2 hours by nasogastric tube. The ranitidine group received 1.5 mg/kg every 6 hours IV. The sucralfate group received 0.5 to 1 g every 6 hours by nasogastric tube. The occurrence rate of important upper gastrointestinal haemorrhage was higher (by 20 %) in the control group than in the rest of the groups (5.7 %), ($p < 0.01$). There were no differences between the other groups (almagate 5.7 %, ranitidine 8.5 %, and sucralfate 2.8 %) [73].

[REDACTED] conducted a prospective, randomized trial comparing cimetidine in a single dose of 800 mg and sucralfate at a dose of 1 g/6h in a group of 139 patients from a cohort of 2,010 patients consecutively admitted during a 10-month period to a department of internal medicine at a teaching hospital. Two of the 71 patients assigned to cimetidine and 2 of the 68 assigned to sucralfate presented with acute gastrointestinal bleeding, which was more severe in the sucralfate group. The drugs had similar safety profiles and were well tolerated [74].

2.5.4.5.2 Stress-Related Mucosal Disease

Several studies have compared the efficacy of sucralfate with antacids or H₂RAs for prophylaxis of stress-related bleeding. Individually each study shows similar or slightly lower rates of stress-related bleeding in those receiving sucralfate compared with antacids or H₂RAs.

A meta-analysis of 42 randomized trials, selected according to prospectively defined criteria and involving 4,409 patients at risk, demonstrated that in reducing the risk of overt bleeding, antacids and H₂-antagonist drugs were superior to placebo or no therapy. Likewise, H₂-antagonists were superior to antacids, and pirenzepine (an M₂-muscarinic-receptor antagonist) was superior to H₂-antagonists [198]. H₂-antagonists were also more effective than antacids in reducing clinically important bleeding (involving hemodynamic instability, a fall in the haemoglobin level by more than 30 g/L, and a requirement for transfusion) [198]. The claims for the efficacy of sucralfate are based not on placebo-controlled studies, but on studies in which sucralfate appeared as effective as antacids and H₂-antagonists.

The mortality rate in patients with stress-induced bleeding that is treated with H₂-antagonists (seven trials) or antacids (two trials) has not been lower than in untreated patients [199]. Of eight trials comparing mortality rates in sucralfate-treated patients with those in patients treated with H₂-antagonists or antacids, seven showed no statistically significant benefit for sucralfate [199].

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2.5.4.6 ESOPHAGITIS

Reflux esophagitis is a chronic disorder characterized by the symptoms of heartburn and regurgitation [200].

At least seven clinical trials have been reported in adult patients in which sucralfate has been compared to monotherapy with another agent, five with an H₂ antagonist [75-79] and two with the alginate-antacid combination [80, 81]. Three of the five studies using an H₂ antagonist for comparison to sucralfate, used cimetidine and two used ranitidine. In essentially all of the studies, the data show equal efficacy in the treatment of reflux disease with sucralfate compared to that of the alternative drug in terms of both symptom relief and lesion healing. Additional studies have been carried out in an attempt to extend the profile of patients for which sucralfate may have benefit. [redacted] tested its ability to improve patients with grades I-IV (Savary classification) who had initially failed a course of an H₂RA; however, sucralfate failed to heal these refractory subjects [82]. Similarly, the ability of a combination of sucralfate with an H₂RA (cimetidine) has been tested to determine if it would achieve superior effects in patients with reflux esophagitis, but in the two trials performed thus far as exemplified by that of [redacted], a beneficial effect on lesion healing has been marginal.

In a study by [redacted], 12 weeks of treatment demonstrated sucralfate to be superior to placebo in the healing of reflux induced lesions (72 versus 40 %, $p < 0.05$), and though symptoms were also improved, the results did not reach statistical significance [84].

Given that oesophageal ulcers commonly occur after endoscopic variceal sclerotherapy, [redacted] investigated the effect of sucralfate granules in suspension on the treatment of endoscopic variceal sclerotherapy induced ulcer. Fifty-two patients with oesophageal variceal bleeding received elective endoscopic variceal sclerotherapy. After endoscopically proved oesophageal ulcers, they were randomized to receive either sucralfate granules in suspension ($n=22$) or antacid ($n=23$). Forty-one ulcers receiving sucralfate and 48 ulcers receiving antacid treatment were evaluated. The clinical characteristics of the ulcers were similar in both groups. The ulcers in patients receiving sucralfate healed faster than those receiving antacid ($p < 0.02$). On analysis of factors affecting ulcer healing, ulcers smaller than 1 cm² ($n=59$) appeared to heal faster than those larger than 1 cm² ($n=30$; $p=0.059$) and shallow ulcers ($n=46$) healed faster than deep ulcers ($n=43$; $p < 0.001$). On multifactorial analysis, ulcer depth was the only factor determining ulcer healing. The ulcer healing effects of sucralfate became more prominent when the ulcer was larger than 1.0 cm² (1.7 ± 0.6 weeks vs 2.3 ± 0.6 weeks, $p=0.011$) and deep (1.7 ± 0.7 weeks vs 2.5 ± 1.0 weeks, $p=0.013$) when compared with those receiving antacid. The data indicated that sucralfate granules in suspension speed the healing of endoscopic variceal sclerotherapy induced ulcer, especially deep and large ulcers [85].

In the study of [redacted] one hundred and forty-one patients with moderate to severe gastro-oesophageal reflux symptoms occurring at least three times per week (but no oesophageal erosions or ulcers at endoscopy) were treated in this randomized, double-blind, placebo-controlled study at six trial centres. Treatment was given for 6 weeks and consisted of daily doses of either 1 g sucralfate gel b.d. or placebo. The evaluation of efficacy was based on data of 139 patients. The responder rate at day 42 was statistically significantly higher for the patients treated with sucralfate (71 %) than for the placebo patients (29 %) ($p < 0.0001$). The overall response of the non-ulcer dyspepsia and gastro-oesophageal reflux disease symptoms was better for sucralfate gel than for placebo with 45 % of patients treated with sucralfate gel being considered as having a "good" or "excellent" overall response compared with 22 % of the patients who received placebo ($p < 0.0001$) [86].

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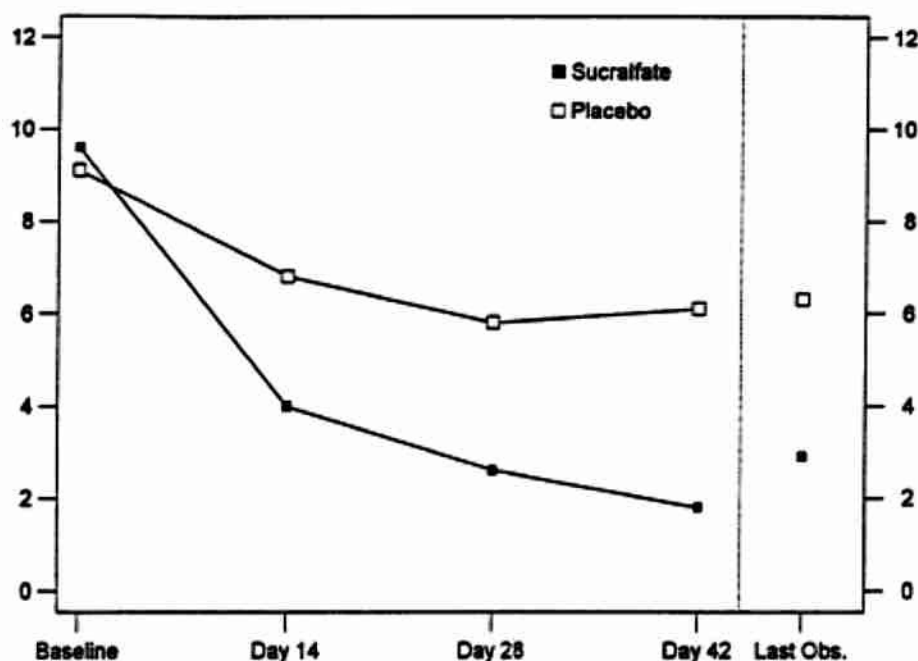


Figure 12 Sum of non-ulcer dyspepsia and GERD symptom scores [86]

A double-blind, multi-centre, randomized study was performed in 75 patients with endoscopically documented reflux esophagitis. Patients were randomly given 1 g sucralfate four times a day or the combination of sucralfate three times a day and 300 mg ranitidine after dinnertime. Endoscopy was performed at the beginning of the study, after 8 weeks, and, if, the reflux esophagitis was not healed, after 16 weeks. Endoscopy showed symptomatic improvement in 67 % of the patients treated with sucralfate and in 74 % of the combination therapy group. Complete healing or Savary-Miller stage 1 was seen in 26.5 % and in 31.4 %, respectively. The authors concluded that sucralfate monotherapy in patients with milder forms of reflux esophagitis is comparable with a combination of sucralfate during the day and ranitidine after dinnertime [87].

2.5.4.7 COMBINED THERAPY WITH H₂-ANTAGONIST DRUGS

Of particular interest is therapy combining sucralfate and an H₂-antagonist drug. No controlled studies show a statistically significant benefit of therapy involving a combination of sucralfate and any H₂-antagonist, as compared with either drug alone, in treating acute duodenal ulcer, in ulcer maintenance therapy, in stress bleeding, or in reflux esophagitis.

2.5.4.8 NOSOCOMIAL PNEUMONIA

Sucralfate leads to a significant reduction of gastric bacterial overgrowth compared with acid-suppressing drugs. This effect can only partly be explained by differences in the gastric pH [201].

Investigating 133 tracheal swabs of patients undergoing long-term ventilation, randomly assigned to sucralfate or ranitidine prophylaxis [88]. They found a significantly higher frequency of tracheobronchial colonization with ranitidine than with sucralfate therapy (43.3 versus 18.6 %). Seventy-three patients ventilated for at least 48 hr were randomly treated with sucralfate, cimetidine,

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or antacids and retrospectively analysed for pneumonia frequency. Twelve percent of patients with sucralfate prophylaxis developed nosocomial pneumonia versus 21 % of patients in both groups with acid suppressing medication. [redacted] compared the pneumonia rate in 104 ICU patients undergoing long-term ventilation with sucralfate or H₂-antagonists (cimetidine) [89]. In the sucralfate group the pneumonia rate was 29 %, in the cimetidine group 46 %.

Another study in 244 ventilated surgical patients comparing sucralfate, antacids, and ranitidine showed a significantly lower pneumonia rate in sucralfate-treated patients. This study proved that only secondary pulmonary infections were reduced by sucralfate but not early onset pneumonia [90].

The frequency of nosocomial pneumonia in ICU patients in relation to stress ulcer prophylaxis is presented in the following figure.

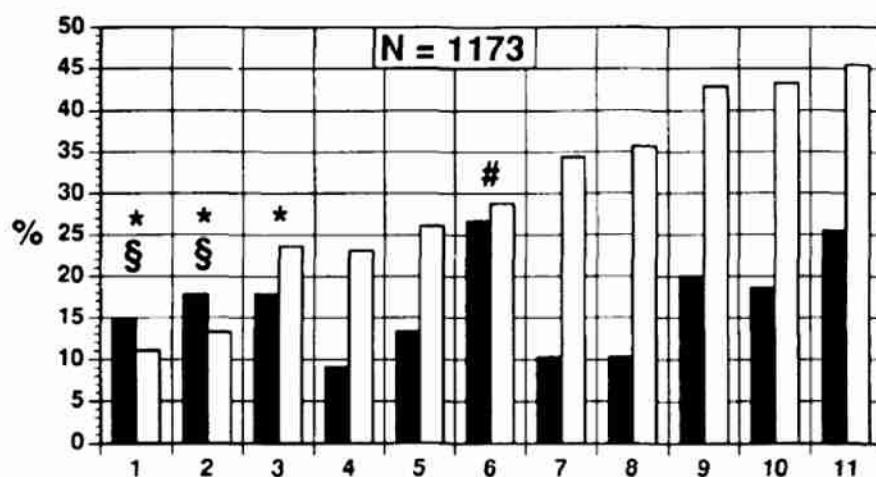


Figure 13 Frequency of nosocomial pneumonia in ICU patients in relation to stress ulcer prophylaxis with sucralfate (■) or antacids/H₂ antagonists (□) (prospective studies through August 1992). *Low-dose H₂ antagonists/antacids; §maximum duration of treatment was 7 days; #no difference in gastric colonization [201]

Sucralfate has been associated with a lower risk of nosocomial pneumonia than pH-elevating antacids or H₂-antagonist drugs [91, 92, 199].

In the study of [redacted] ninety-eight injured patients who were critically ill and who required intubation and ICU support for at least 72 hours without gastric feeding were randomized and received either maximal H₂ blocker infusion therapy (continuous infusion of ranitidine at 0.25 mg/kg/hr after a loading dose of 0.5 mg/kg) plus antacids (for persistent pH<4) or sucralfate (1 g every 6 hours via nasogastric tube) for stress ulcer prophylaxis. The overall pneumonia rate was 27.5% in the H₂ blocker group and 20.8 % in the sucralfate group (p=0.48). Days on ventilator were 13.5 versus 9.1, (p=0.06), ICU lengths of stay were 14.7 versus 10.2 (p=0.06), and hospital lengths of stay were 27.8 versus 20.0 (p=0.029) for the H₂ blocker group and sucralfate group, respectively [93].

Pulmonary infections are common in patients with indwelling stomach tubes who are receiving antacids, particularly during mechanical ventilation [202]. A retrospective study of risk factors for pneumonia in 233 patients receiving mechanical ventilation showed an odds ratio of 2.5 (95 % CI, 1.2 to 5.0) for cimetidine use as a risk factor; whether this association was causal or whether it simply reflected the use of cimetidine in the sickest patients was not evaluated.

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██████████ compared the effectiveness of non-acid neutralizing SUC with sucralfate (n=48) with that of AN prophylaxis utilizing antacids and cimetidine (n=48) in the prevention of stress ulcer bleeding and PN in thermally injured patients. In the subset of intubated patients, the incidence of PN was 17.8 % and 42.8 % in the AN and SUC groups, respectively ($p<0.05$) despite a similar postburn time of onset of pneumonia. Bacterial colonization of the upper airway occurred in virtually all patients, whereas 83 % (SUC) and 96 % (AN) had colonization of gastric contents. Gram-negative colonization rates for the upper airway were not different (70 %) whereas 48 % of SUC patients compared with 60 % of AN patients had gram-negative gastric colonization [94].

Two prospective studies have compared the risk of nosocomial pneumonia in patients receiving mechanical ventilation who were treated with sucralfate with the risks in similar patients treated with antacids [95] or with either antacids or H_2 -antagonists [91]. In the first study, pneumonia developed in more patients treated with antacids than patients treated with sucralfate (34 vs. 10 %, $p<0.05$) [95]. The results of the second study were similar, but the difference was not significant (23 vs. 12 % for the risks with antacids and sucralfate, respectively); the lowest risk (6 %) was found with the use of H_2 -antagonists [91]. By grouping antacids and H_2 -antagonists together as alkalinizing agents and excluding from the analysis six patients who were changed to the opposite treatment, the authors claimed that sucralfate was less hazardous than therapy with antacids or H_2 -antagonists when these treatment groups were combined ($p=0.05$).

Whether nosocomial pneumonia more often accompanies the use of H_2 -antagonists or that of sucralfate is clinically important. In one well-designed trial, a continuous infusion of cimetidine (900 mg/day in 56 patients) was compared with an infusion of placebo (in 61 patients); placebo, but not cimetidine, was associated with nosocomial pneumonia. In another trial, an infusion of cimetidine (900 mg/day) was compared with a sucralfate suspension (1 g four times daily); the rates of bleeding, pneumonia, and mortality did not differ significantly between groups [96]. Finally, a meta-analysis of outcomes in 493 patients revealed that prophylaxis for stress ulcers with drugs that raised the intragastric pH did not increase the incidence of pneumonia in comparison with placebo or no therapy [203].

That sucralfate is safer than antacids appear likely; the reason is less clear. Previous studies advanced the hypothesis that as gastric pH values increase above 3.5, gram-negative flora increase in the stomach, and their aspiration would then lead to pneumonia [95]. High pH values should thus be found mainly in patients treated with antacids or H_2 -antagonists, but not in those treated with sucralfate. No actual values for intragastric pH were reported, but from one study [95] it can be calculated that the pH exceeded 3.5 in 77 % of the sucralfate-treated patients and 4.5 in 54 %, casting doubt on the hypothesis that differences between sucralfate and other agents, if they exist, can be explained by sucralfate's lack of effect on gastric pH. In fact, patients in the intensive care unit, especially those with hypotension, frequently have diminished output of gastric acid [204, 205], and increased acid secretion can be demonstrated consistently only in patients with intracranial lesions [206, 207].

Sucralfate has been reported to have activity against both gram-negative and gram-positive organisms in the gastric contents of patients in the intensive care unit [199], - an effect beyond that assumed in the biologic hypothesis linking nosocomial pneumonia with reduced gastric acidity.

In the study of ██████████ sixty adult patients who were mechanically ventilated and at risk of developing stress ulceration were randomized to receive either sucralfate (1 g every 6 hrs) via the nasogastric tube or IV ranitidine (50 mg every 6 hrs). On admission, the frequency rate of erosion/ulceration (assessed with the endoscope) was 13.5 %. After 4 days, this rate had increased to

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18 % in sucralfate-treated patients and 36% in ranitidine-treated patients (NS). Mean gastric pH was more alkaline in the ranitidine-treated patients (5.50) compared with the sucralfate-treated patients (4.26) ($p<0.01$). This pH permitted a higher occurrence rate of gastric colonization by aerobic Gram-negative bacilli in ranitidine-treated patients (64.3 %) compared with sucralfate-treated patients (23.8 %) ($p<0.01$). Retrograde bacterial colonization from the stomach to oropharynx and trachea occurred more frequently in ranitidine-treated patients compared with sucralfate-treated patients. Ultimately, the occurrence rate of pneumonia was greater in the ranitidine-treated (35.7 %) than in the sucralfate-treated patients (10.3 %) ($p<0.05$) [97].

In the prospective, randomized trial of [REDACTED] Thirty-nine patients received sucralfate and 44 patients received intravenous ranitidine for stress ulcer prophylaxis. There were no significant differences in demographics, mechanisms of injury, Trauma Score, Injury Severity Score, APACHE score, length of hospital stay, length of surgical intensive care unit stay, or duration of endotracheal intubation between the sucralfate and ranitidine groups. Eleven (13.2 %) patients developed nosocomial pneumonia: six (15.4 %) of 39 patients in the sucralfate group and five (11.4 %) of 44 patients in the ranitidine group; these numbers were not significantly different ($p=0.8805$) [208].

[REDACTED] assessed three anti-stress ulcer prophylaxis regimens in mechanically ventilated patients for bacterial colonization, early- and late-onset nosocomial pneumonia, and gastrointestinal bleeding [90]. Of 244 assessable patients, macroscopic gastric bleeding was observed in 10 %, 4 %, and 6 % of patients assigned to receive sucralfate, antacid, and ranitidine, respectively ($p>0.2$). The incidence of early-onset pneumonia was not statistically different among the three treatment groups ($p>0.2$). Among the 213 patients observed for more than 4 days, late-onset pneumonia was observed in 5 % of the patients who received sucralfate compared with 16 % and 21 % of the patients who received antacid or ranitidine, respectively ($p=0.022$). Mortality was not statistically different among the three treatment groups. Patients who received sucralfate had a lower median gastric pH ($p<0.001$) and less frequent gastric colonization compared with the other groups ($p=0.015$). Using molecular typing, 84 % of the patients with late-onset gram-negative bacillary pneumonia were found to have gastric colonization with the same bacteria before pneumonia developed [90].

In a multi-centre, randomized, blinded, placebo-controlled trial, [REDACTED] compared sucralfate with the H₂-receptor antagonist ranitidine for the prevention of upper gastrointestinal bleeding in 1,200 patients who required mechanical ventilation. Patients received either nasogastric sucralfate suspension (1 g every six hours) and an intravenous placebo or intravenous ranitidine (50 mg every eight hours) and a nasogastric placebo. The patients in the two groups had similar base-line characteristics. Clinically important gastrointestinal bleeding developed in 10 of 596 (1.7 %) of the patients receiving ranitidine, as compared with 23 of 604 (3.8 %) of those receiving sucralfate (relative risk, 0.44; 95 % CI, 0.21 to 0.92; $p=0.02$). In the ranitidine group, 114 of 596 patients (19.1 %) had ventilator-associated pneumonia, as compared with 98 of 604 (16.2 %) in the sucralfate group (relative risk, 1.18; 95 % CI, 0.92 to 1.51; $p=0.19$). There was no significant difference between the groups in mortality in the ICU (23.5 % in the ranitidine group and 22.9 % in the sucralfate group) or the duration of the stay in the ICU (median, nine days in both groups) [98].

The study of [REDACTED] also concluded that in ICU patients, sucralfate is as effective as ranitidine, in the prevention of stress ulceration and gastric bacterial colonization is significantly reduced with substantial reduction in the frequency of secondary pneumonias. Therefore, the routine use of sucralfate as prophylaxis for stress ulceration and gastrointestinal bleeding in ICU patients is recommended [209].

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One hundred forty patients entered the study of [REDACTED] before major elective surgery, allowing baseline cultures of gastric and pulmonary secretions to be obtained intraoperatively. Gastric pH was affected by the form of stress ulcer prophylaxis throughout the study, and this pH effect affected the number of new gastric organisms appearing in the 2 different groups (antacid-treated and sucralfate-treated). Colonization of the airway with new gastric organisms occurred more frequently in the antacid than in the sucralfate group, and colonization of the airway with organisms of gastric origin was associated with occurrence of postoperative pneumonia [99].

2.5.4.9 MISCELLANEOUS USES

In patients with duodenal but not gastric ulcers associated with the use of NSAIDs, the ulcers are equally likely to be healed with sucralfate (1 g four times daily) or ranitidine (150 mg twice daily), whether or not the NSAID therapy is continued [43, 210]. Sucralfate is significantly superior to placebo in reducing the frequency [100] and intensity [100], of dyspeptic symptoms during NSAID therapy. It does not appear to prevent NSAID-associated gastric or duodenal ulcers or their complications, nor does it lower the associated morbidity and mortality [210]. Sucralfate has no demonstrated place in the prevention or therapy of an NSAID associated gastric ulcer or its complications [210, 211].

[REDACTED] assessed whether sucralfate can prevent or diminish short-term NSAID-induced damage in the stomach and duodenum. Sixteen healthy subjects were randomly treated for 7 days with sucralfate 2 g b.d. or placebo in a double-blind cross-over manner. Naproxen 500 mg b.d. was given on days 3-7. Gastrointestinal endoscopy was performed before and after each treatment period. Mucosal damage was measured by counting erosions, submucosal haemorrhages or ulcers on a fixed-point scale of 0-4 for stomach and duodenum separately. The mean posttreatment injury score in the stomach was 2.13 ± 1.51 and 2.0 ± 0.97 for the placebo and sucralfate periods, respectively ($p=0.72$). The possibility of type II error was 7 %. In the duodenum, the injury score was 1.69 ± 1.08 and 1.06 ± 0.93 for the placebo and sucralfate periods, respectively ($p=0.08$). The possibility of type II error was 37 % [101].

A randomized, double-blind, placebo-controlled, multi-centre study was conducted by Malagelada et al (2003) to assess the efficacy of 2 g sucralfate suspension in treating gastric mucosal lesions caused by long-term treatment with NSAIDs. Twenty-five patients received sucralfate and 25 received placebo. At the end of the study, 68 % (17/25) of patients given sucralfate had no lesions (Lanza grade 0) on endoscopy compared with 35 % (8/23) in controls ($p=0.042$). The Lanza grades in patients given sucralfate were significantly improved compared with the placebo patients ($p=0.022$). Chronic administration of sucralfate significantly decreased NSAID-induced gastric erosions [102].

More than 20 clinical trials have evaluated sucralfate therapy in patients with gastroesophageal reflux disease. Among the controlled studies, only one comparison of sucralfate with placebo showed a significant reduction of symptoms [103], and one showed significantly better healing with sucralfate than with placebo [84]. Overall, when comparisons of active treatment with H_2 -antagonists or open-label studies are included, the drug seems modestly effective in nonerosive oesophageal disease. Controlled trials of its efficacy in healing after sclerotherapy and the treatment of other oesophageal ulcers show no benefit [104, 105].

[REDACTED] coordinated a multi-center randomized trial including 500 patients with dyspeptic symptoms and endoscopic features of nonerosive gastritis comparing an 8-week treatment with either sucralfate or ranitidine [106]. Both drugs induced a significant reduction in the endoscopic severity score, sucralfate being significantly more effective ($p<0.02$) in promoting healing or improvement of

2.5 Clinical overview

endoscopic gastritis. Sucralfate was also superior in promoting normalization of histological features ($p<0.001$). Dyspeptic symptoms were eliminated in the majority of patients by both drugs which appeared to be equally effective in this respect. However, during the first 4 weeks of therapy the number of patients becoming symptom-free was significantly higher ($p<0.01$) with ranitidine, confirming the notion that H_2 -receptor antagonists relieve symptoms faster than gastroprotective agents.

investigated the effects of sucralfate on acute gastric and duodenal injury and on changes in intragastric bleeding induced by aspirin. On three occasions, 24 healthy volunteers received three days' treatment with aspirin 900 mg twice daily together with placebo, sucralfate 2 g twice daily or sucralfate 1 g four times daily. Aspirin significantly inhibited ex vivo gastric mucosal PGE_2 synthesis, reduced serum thromboxane, caused gastric erosions, and increased spontaneous and biopsy induced bleeding. Sucralfate 1 g four times daily significantly reduced spontaneous, and biopsy induced bleeding. Similar trends were seen with sucralfate 2 g twice daily [107].

2.5.4.10 DOSAGE AND ADMINISTRATION

2.5.4.10.1 Duodenal ulcer, gastric ulcer, chronic gastritis

2.5.4.10.1.1 *Adults*

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.

The maximum daily dose is 8 grams.

Four to six weeks' treatment is usually needed for ulcer healing, but up to twelve weeks may be necessary in resistant cases.

Antacids may be used as required for relief of pain but should not be taken half an hour before or after sucralfate.

2.5.4.10.1.2 *Paediatric population*

The safety and efficacy of sucralfate in children under 14 years of age has not been established.

2.5.4.10.1.3 *Elderly*

There are no special dosage requirements for elderly patients but as with all medicines, the lowest effective dose should be used.

2.5.4.10.2 Prophylaxis of gastrointestinal haemorrhage from stress ulceration

2.5.4.10.2.1 *Adults*

The usual dose is 1 gram six times a day. A maximum dose of 8 grams daily should not be exceeded. Antacids may be used as required for relief of pain but should not be taken half an hour before or after sucralfate.

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2.5.4.10.2.2 Elderly

There are no special dosage requirements for elderly patients but as with all medicines, the lowest effective dose should be used.

2.5.4.10.2.3 Paediatric population

The safety and efficacy of sucralfate in children under 14 years of age has not been established.

2.5.5 OVERVIEW OF SAFETY

2.5.5.1 TOXICITY

2.5.5.1.1 Adverse Events

Sucralfate is generally well tolerated. The most frequent adverse effect of sucralfate is constipation, which reportedly occurs in about 2 % of patients receiving the drug. Other adverse effects of sucralfate reportedly occur in less than 1 % of patients and include diarrhoea, nausea, vomiting, gastric discomfort, flatulence, indigestion, dry mouth, rash, pruritus, back pain, headache, dizziness, insomnia, sleepiness, and vertigo. Adverse reactions requiring discontinuance of the drug occur rarely. Hypersensitivity reactions such as urticaria (hives), angioedema, respiratory difficulty, and rhinitis have been also reported with sucralfate tablets. Similar reactions have been reported with sucralfate suspension. In addition, laryngospasm and facial swelling have been reported with sucralfate suspension, but a causal relationship has not been established [212].

Bezoars have been reported with sucralfate therapy. Most patients who developed bezoars had underlying medical conditions that may have predisposed to bezoar formation (e.g., delayed gastric emptying) or were receiving concomitant enteral tube feedings [212].

2.5.5.1.2 Precautions and Contraindications

Since duodenal ulcer is a chronic recurrent disease, successful therapy with sucralfate should not be expected to alter the post-healing frequency of recurrence or the severity of duodenal ulceration.

Small amounts of aluminum are absorbed from the GI tract when sucralfate is administered orally. Concomitant use of sucralfate with other products that contain aluminum (e.g., aluminum-containing antacids) also can increase the total body burden of aluminum. In patients with normal renal function, this increased body burden of aluminum is excreted in the urine; however, patients with chronic renal failure or those receiving dialysis treatment may not adequately excrete the absorbed aluminum. In addition, because the absorbed aluminum is bound to plasma proteins (e.g., albumin, transferrin) and is not dialyzable, accumulation and intoxication (e.g., aluminum osteodystrophy, osteomalacia, encephalopathy) can occur in patients with impaired renal function. Therefore, sucralfate should be used with caution in patients with chronic renal failure [213].

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2.5.5.1.3 Special Populations

2.5.5.1.3.1 *Use in the Elderly*

There are no special dosage requirements for elderly patients but as with all medicines, the lowest effective dose should be used.

2.5.5.1.3.2 *Use in Children*

The safety and efficacy of sucralfate in children under 14 years of age has not been established.

2.5.5.1.3.3 *Use in hepatic and renal impairment*

Aluminium osteodystrophy, osteomalacia, encephalopathy, and anaemia have been reported in patients with chronic renal impairment. For patients with impairment of renal function, laboratory testing such as aluminium, phosphate, calcium, and alkaline phosphatase is recommended to be periodically performed due to excretion impairment [214].

2.5.5.1.3.4 *Fertility, Pregnancy and Lactation*

Safety in pregnant women has not been established, and sucralfate suspension should be used during pregnancy only if clearly needed. It is not known whether sucralfate is excreted in human milk. Caution should be exercised when sucralfate is administered to breast-feeding women.

2.5.5.1.4 Effects on Ability to Drive and Use Machines

Driving or use of machines should be avoided.

2.5.5.1.5 Overdose and Treatment

In a clinical trial on healthy men of overdose with sucralfate, most cases remained asymptomatic, but symptoms of abdominal pain, nausea, and vomiting were reported in a few cases. Acute oral toxicity studies in animals, using doses up to 12 g/kg body weight, could not find a lethal dose [212].

2.5.6 BENEFITS AND RISKS CONCLUSIONS

2.5.6.1 THERAPEUTIC CONTEXT

2.5.6.1.1 Disease or Condition

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. This disease occurs when the protective mechanisms of the gastrointestinal mucosa are affected by the destructive effects of stomach acid and pepsin. On the other hand, ulcers may develop in unusual areas, such as the ileum, due to Meckel's diverticulum, inlet patch in the proximal oesophagus, or in the jejunum due to excessive acid secretion in Zollinger-Ellison syndrome.

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2.5.6.1.2 Current Therapies

H₂-receptor antagonists or PPIs are also effective treatments for the peptic ulcers. Mucosal protective drugs such as rebamipide and polaprezinc are also used.

2.5.6.2 BENEFITS

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.

2.5.6.3 RISKS

Sucralfate acts locally with negligible absorption, making it relatively safe. The most common side effect is constipation, seen in 1 % to 10 % of patients. Hyperglycaemia is also reported in diabetic patients using sucralfate. Other adverse effects include nausea, vomiting, flatulence, headache, dry mouth, pruritis, skin rash, gastric bezoar formation, aluminum intoxication, and hypophosphatemia. Inadvertent IV use of sucralfate has caused fatal complications such as pulmonary emboli and cerebral oedema.

Long-term users of sucralfate are shown to retain negligible levels of aluminum, except when a patient has renal insufficiency. Uraemia causes increased absorption of aluminum from the gut, and the quantity of aluminum absorbed is similar to that of aluminum hydroxide. Sucralfate should be used cautiously in patients with end-stage renal disease or avoided altogether to prevent aluminum intoxication.

Risks associated with sucralfate overdosing are minimal as sucralfate has minimal absorption from the gastrointestinal system; many patients who overdosed on sucralfate remained asymptomatic. Due to the small amount of aluminum absorbed with oral intake of sucralfate, it can cause aluminum accumulation and toxicity in patients with chronic kidney disease or those receiving dialysis.

2.5.6.4 BENEFIT-RISK ASSESSMENT

Sucralfate has been compared with placebo and cimetidine in reasonably designed trials employing endoscopic evaluation. Based on clinical trials results, surveillance studies and published reports, sucralfate seems to be the safest drug available in the short and long-term treatment of dyspeptic disorders.

Sucralfate has a well-established pharmacological and clinical profile. The active substance is in use for over 40 years.

The results of the in vitro equivalence studies indicate that the product under assessment is expected to exhibit similar in vivo behaviour with the reference formulation.

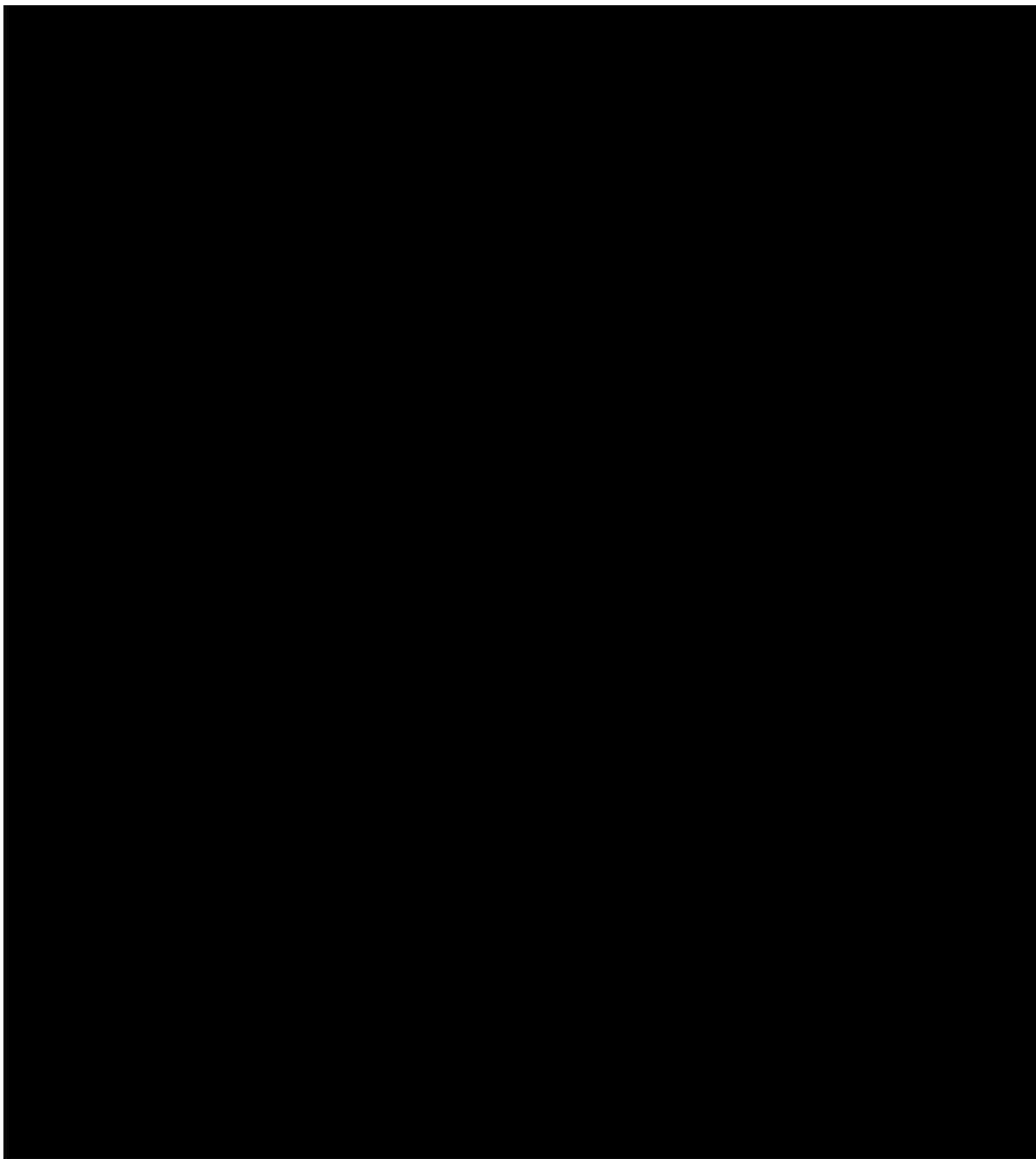
2.5 Clinical overview

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

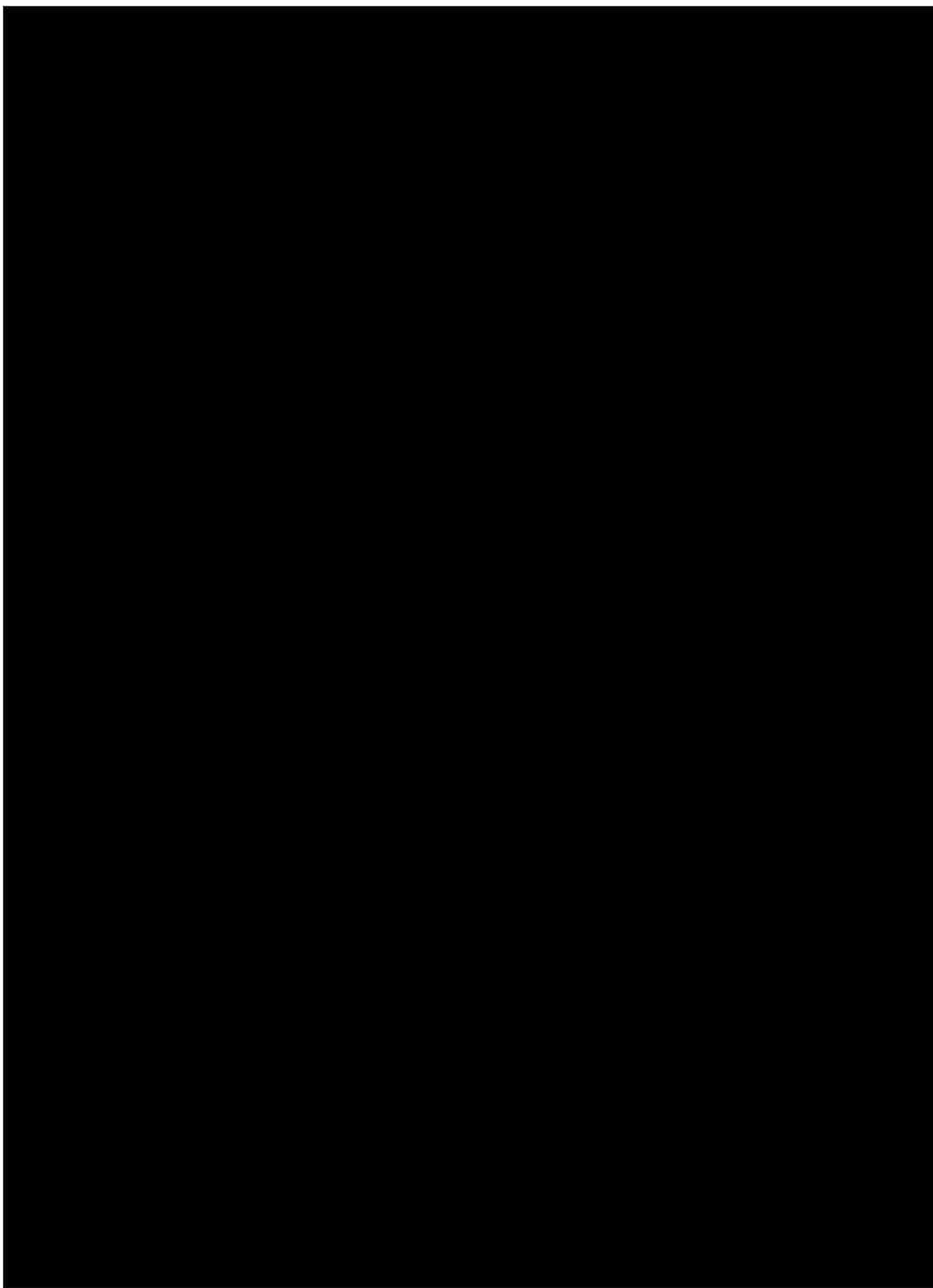
2.5.6.5 APPENDIX

Not applicable.

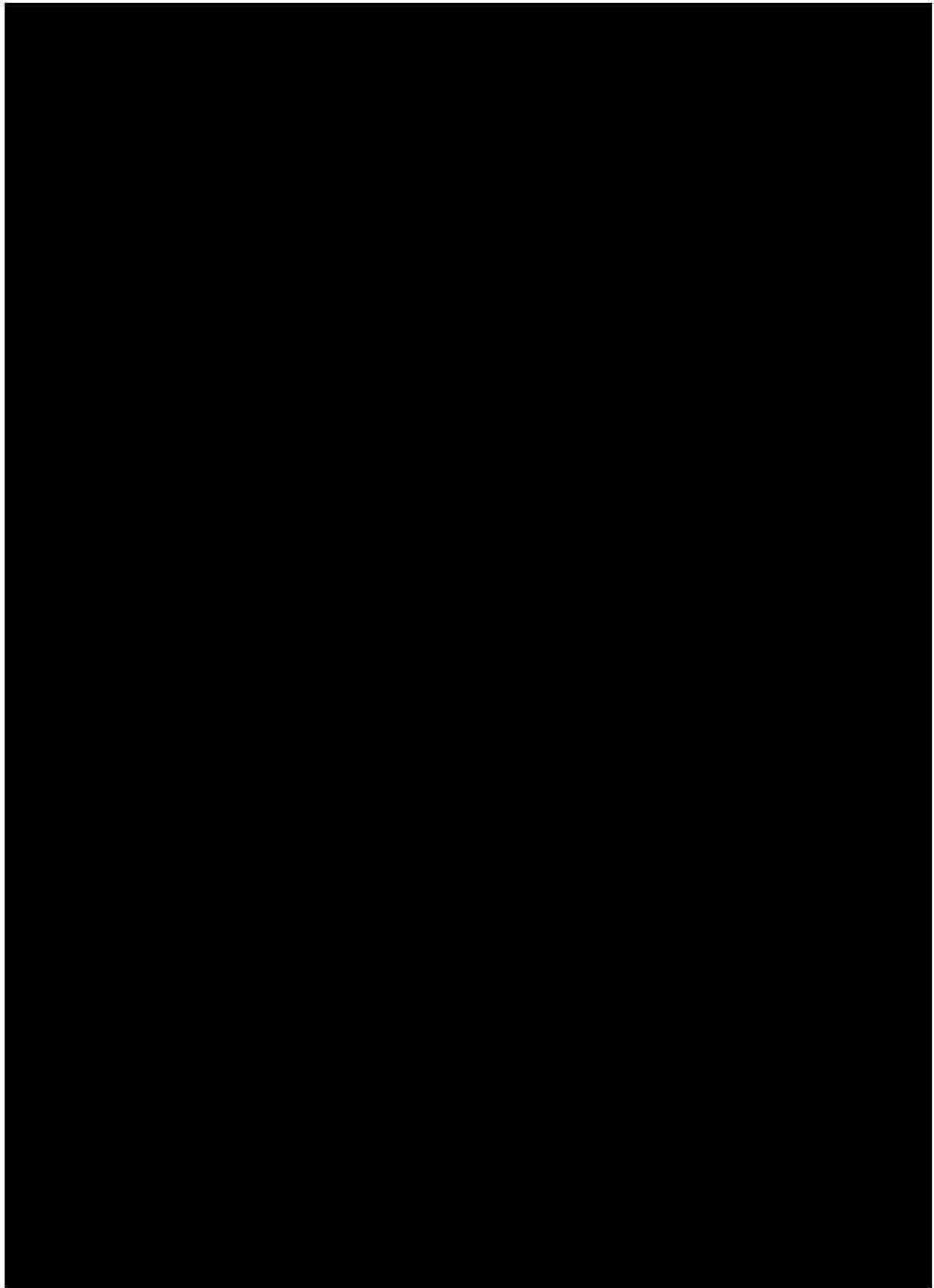
2.5.7 LITERATURE REFERENCES



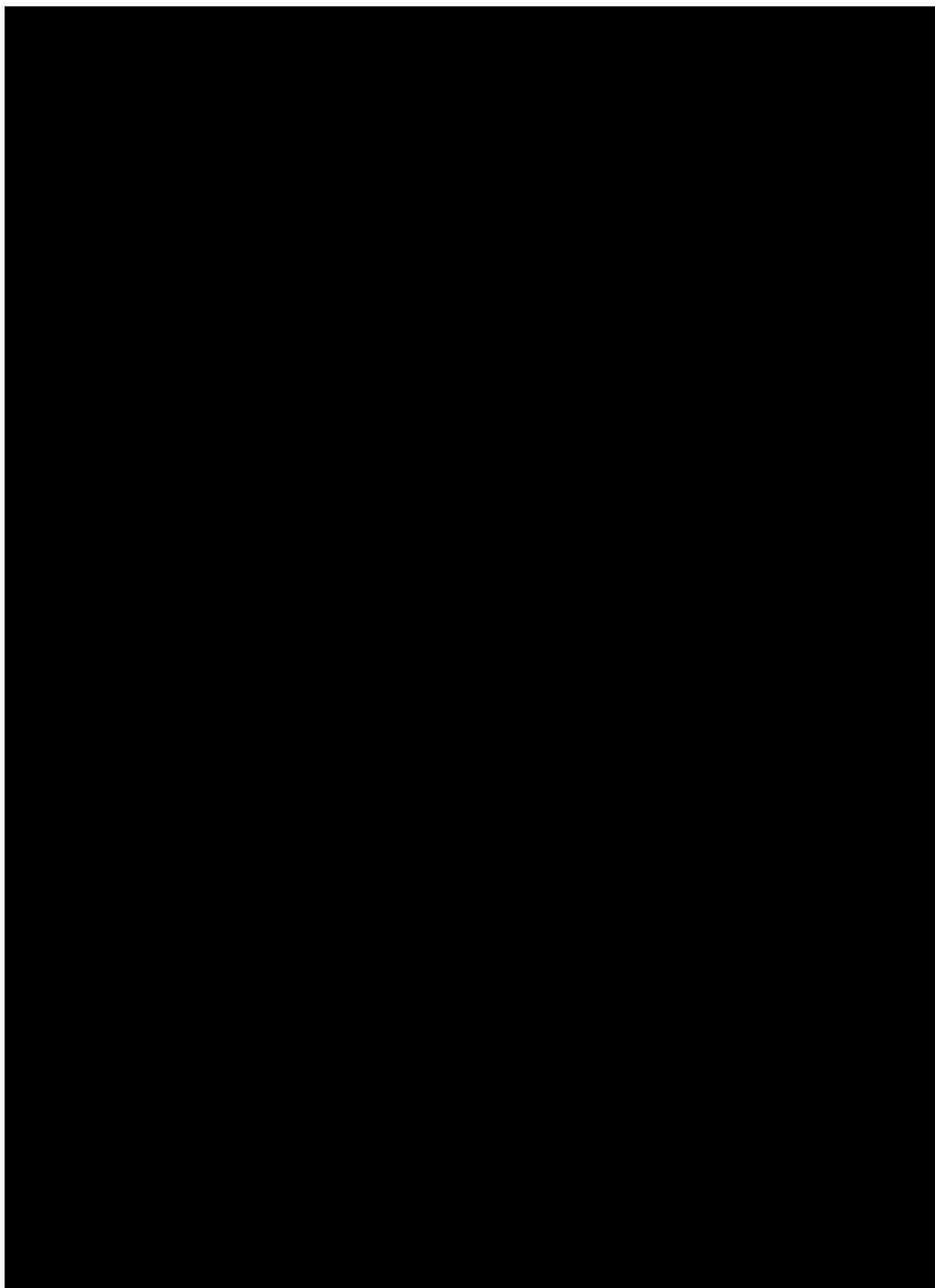
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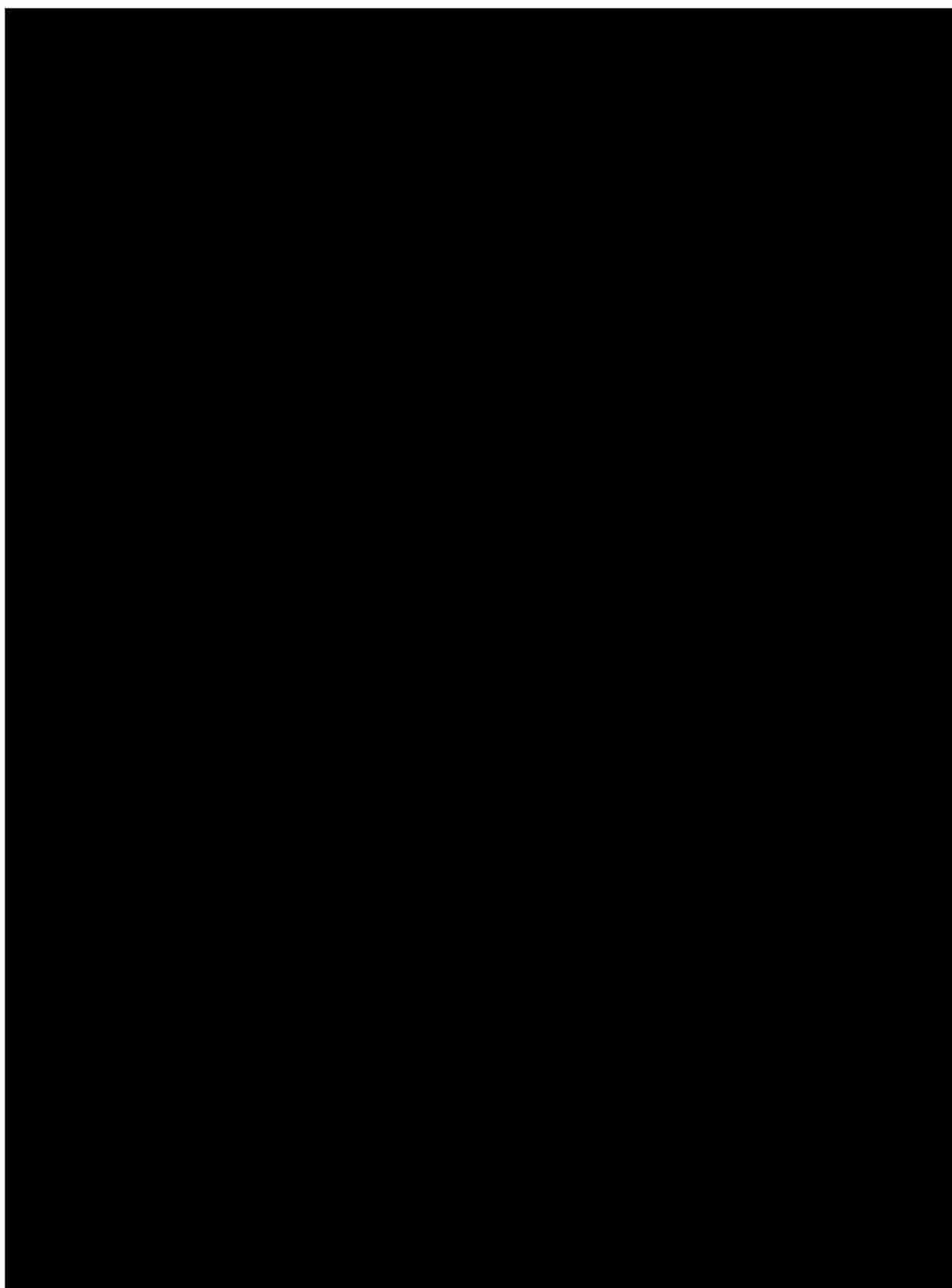
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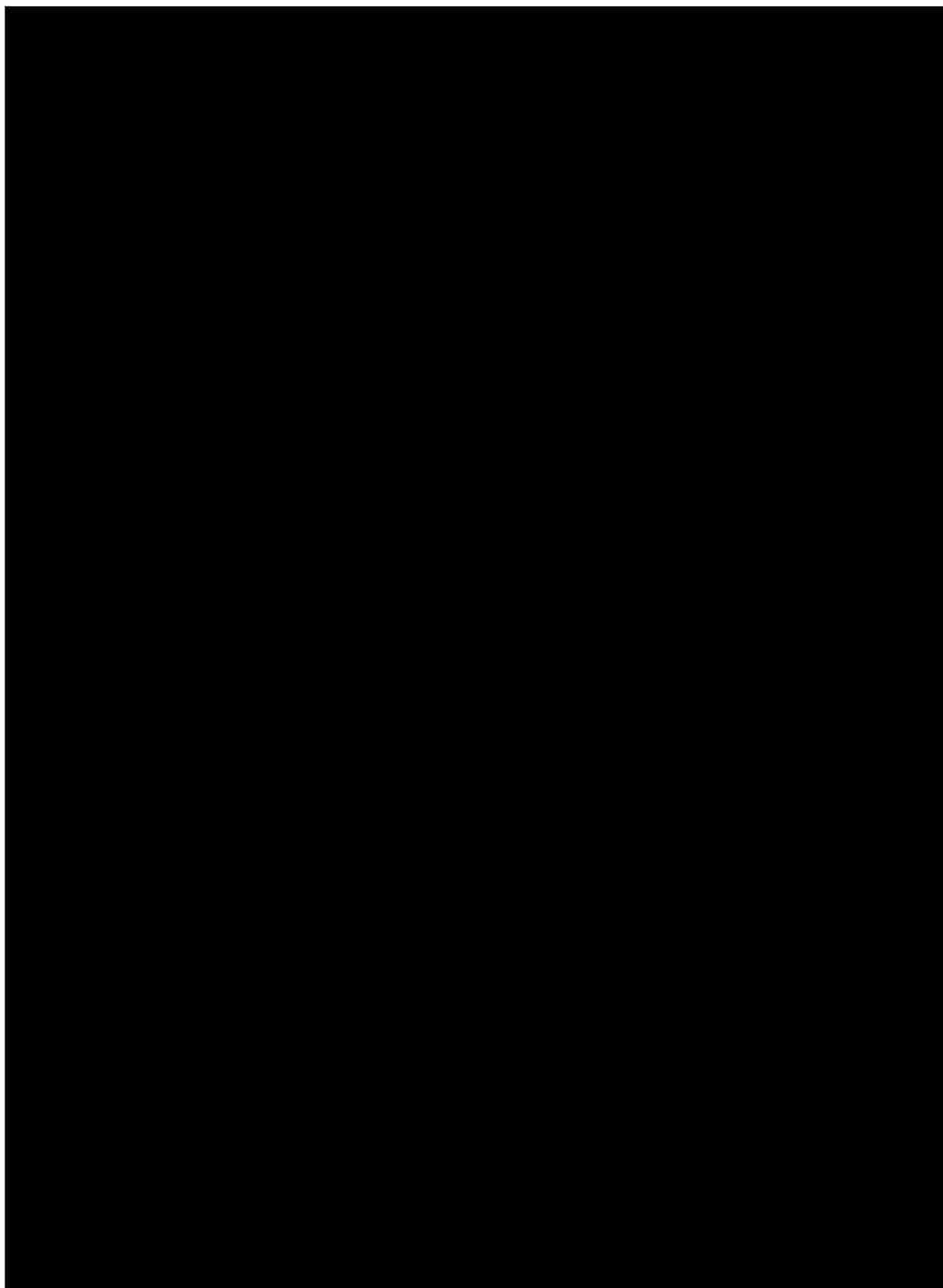
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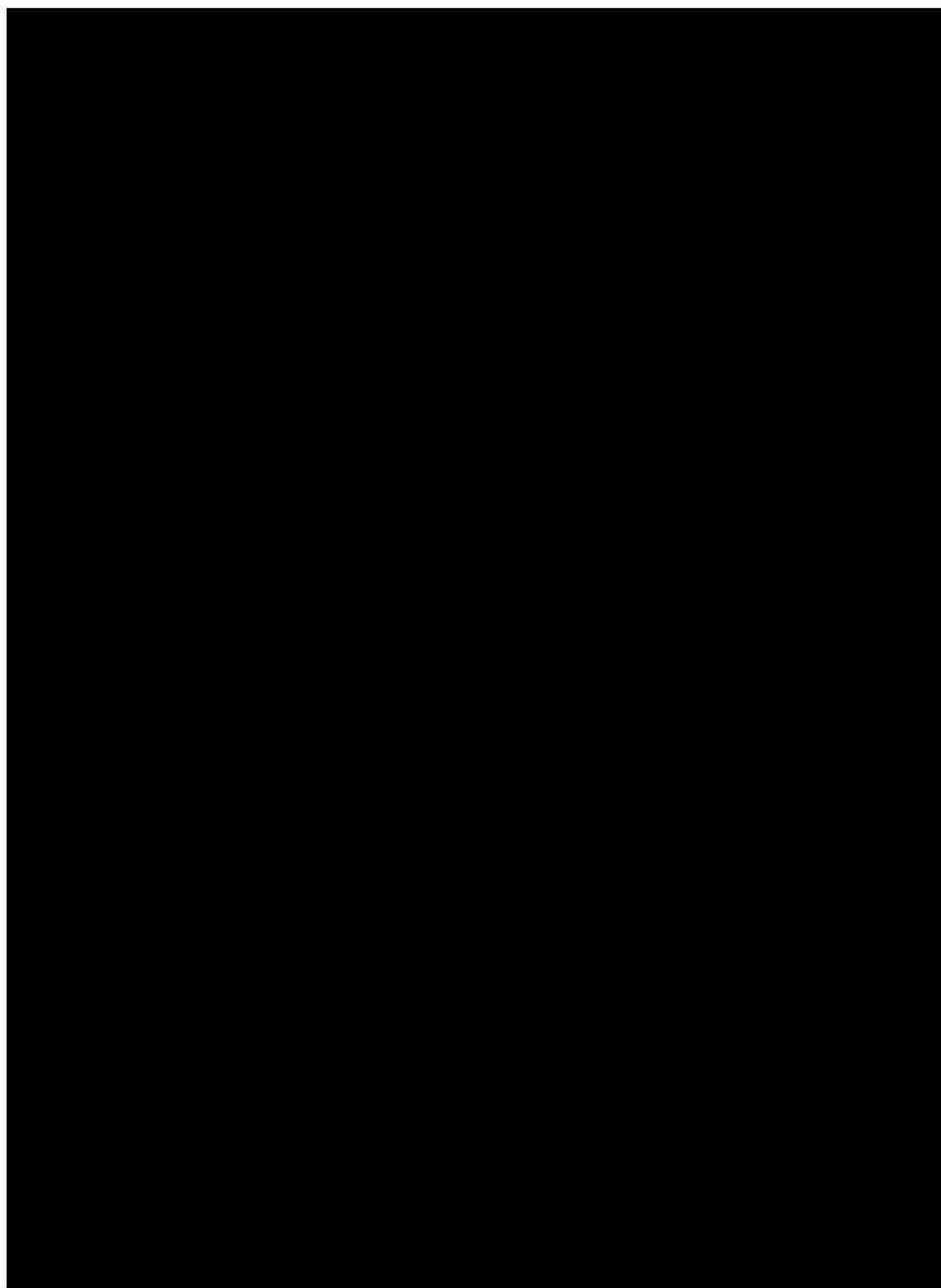
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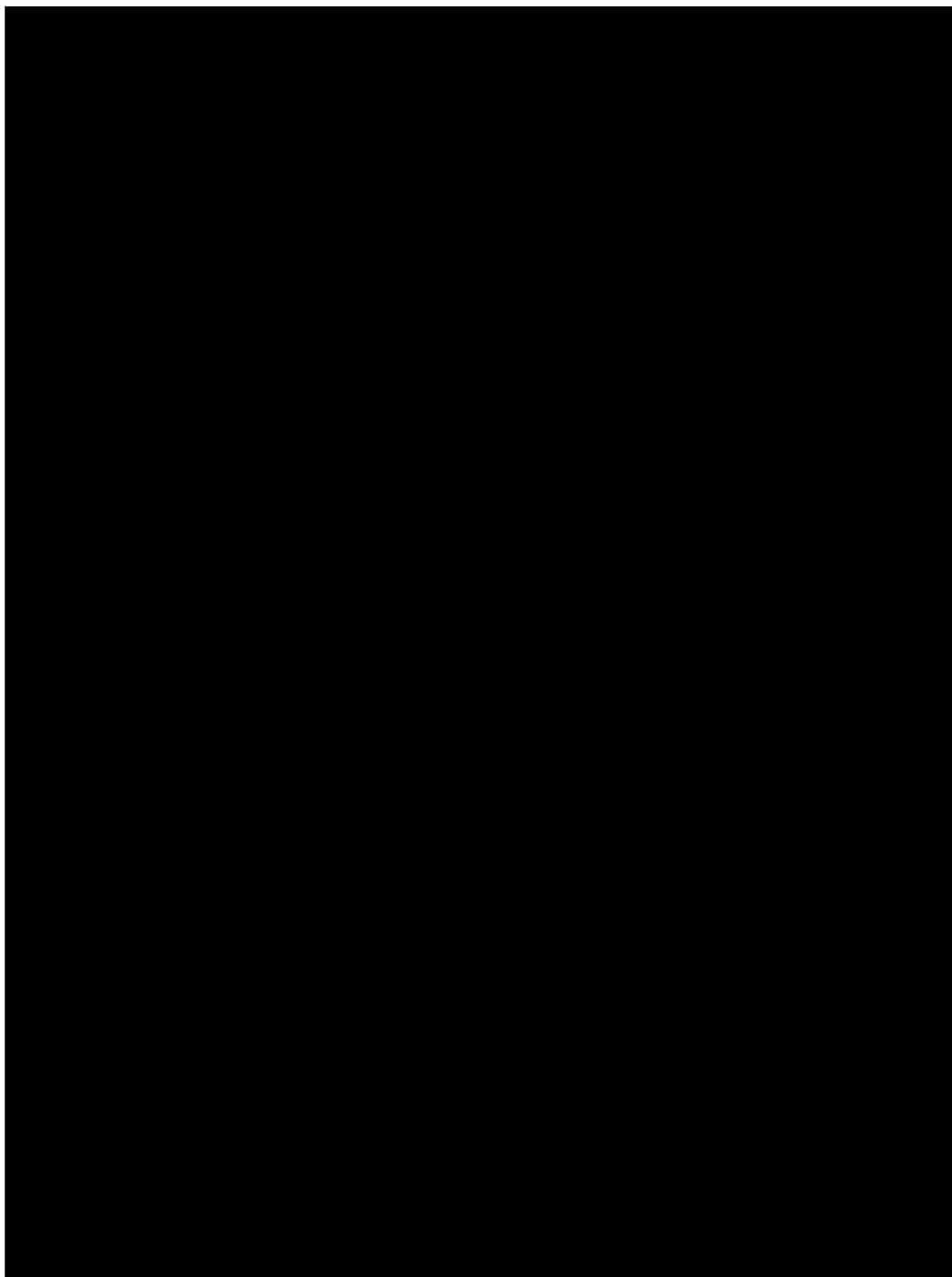
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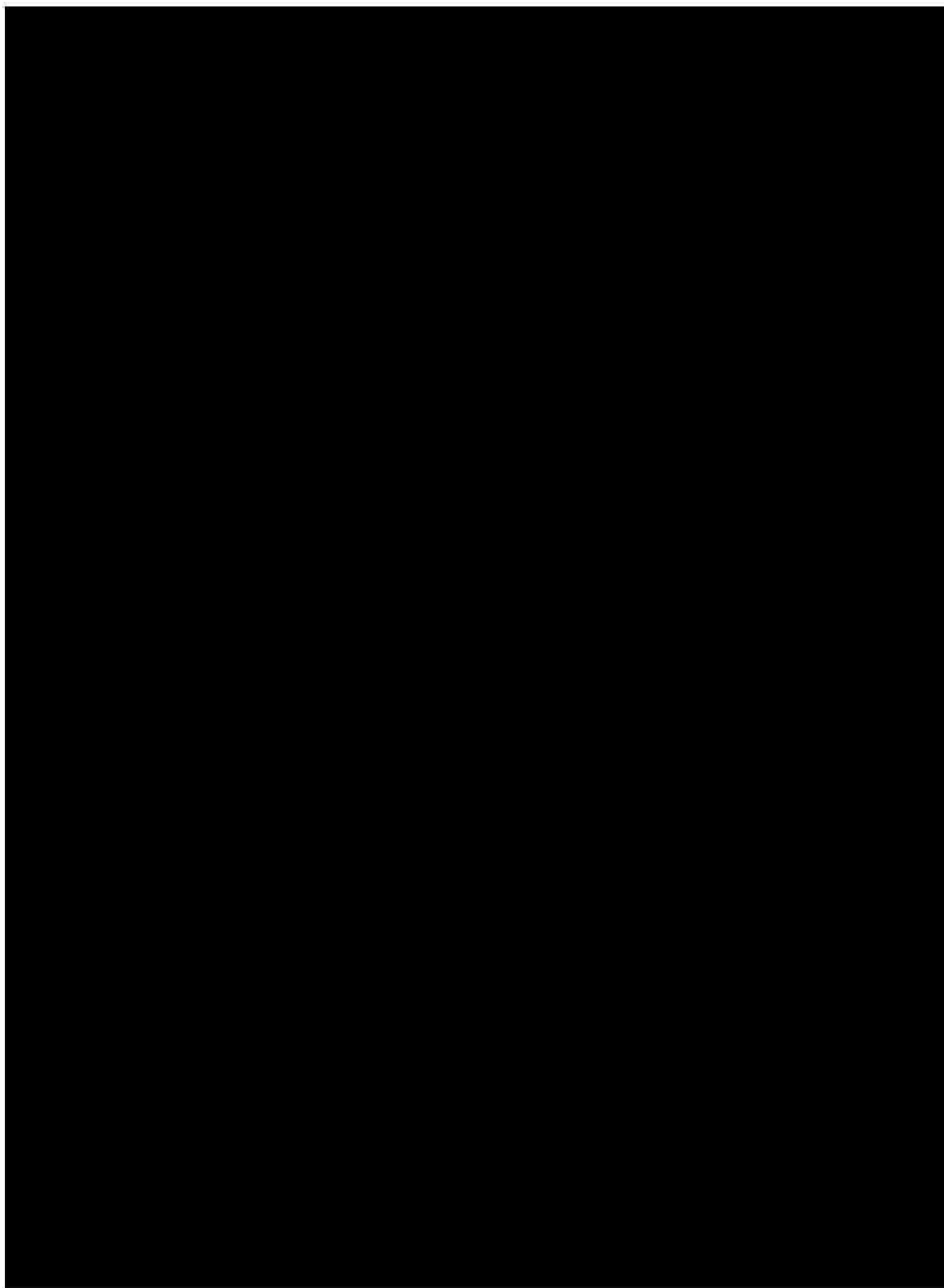
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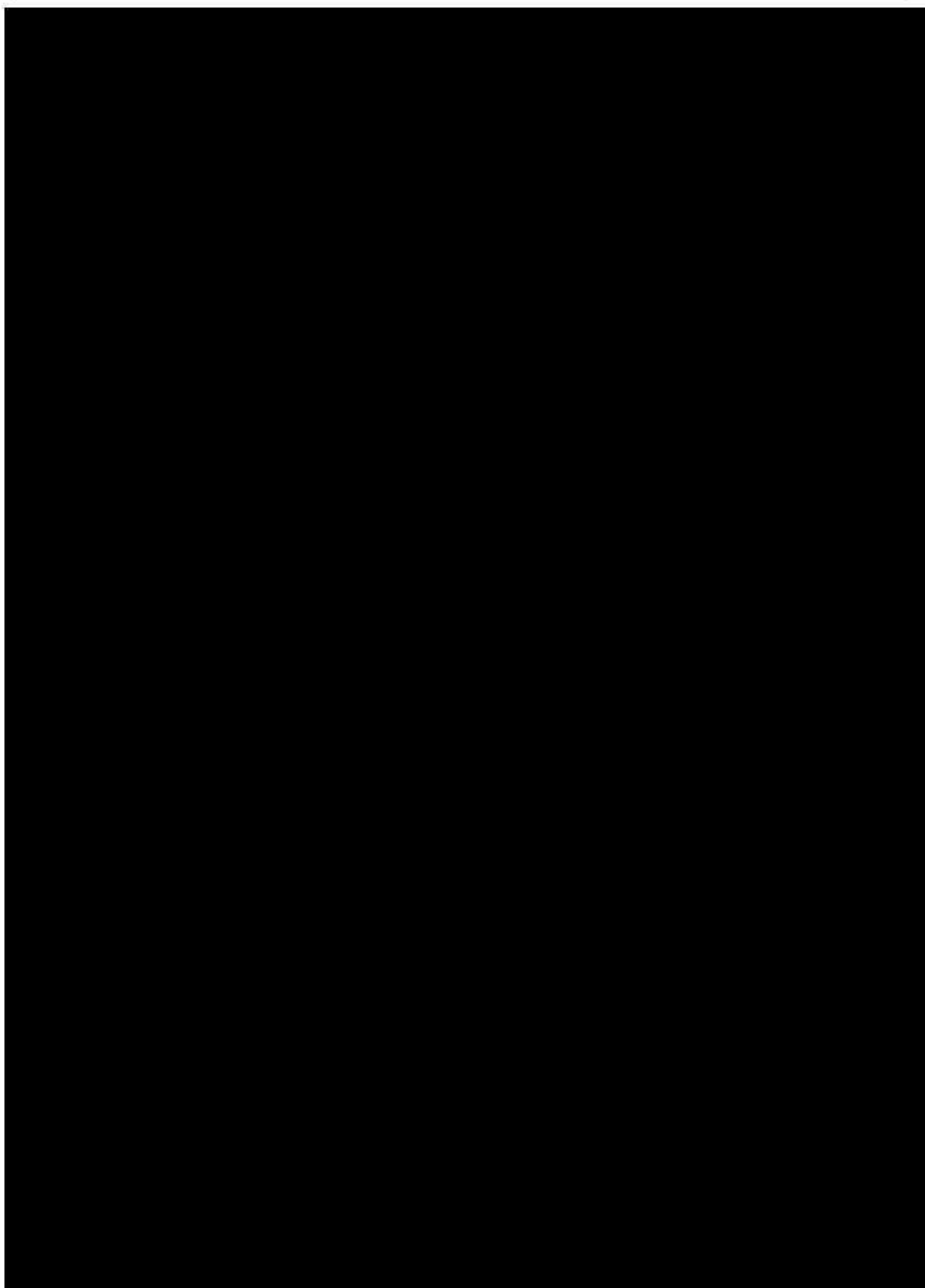
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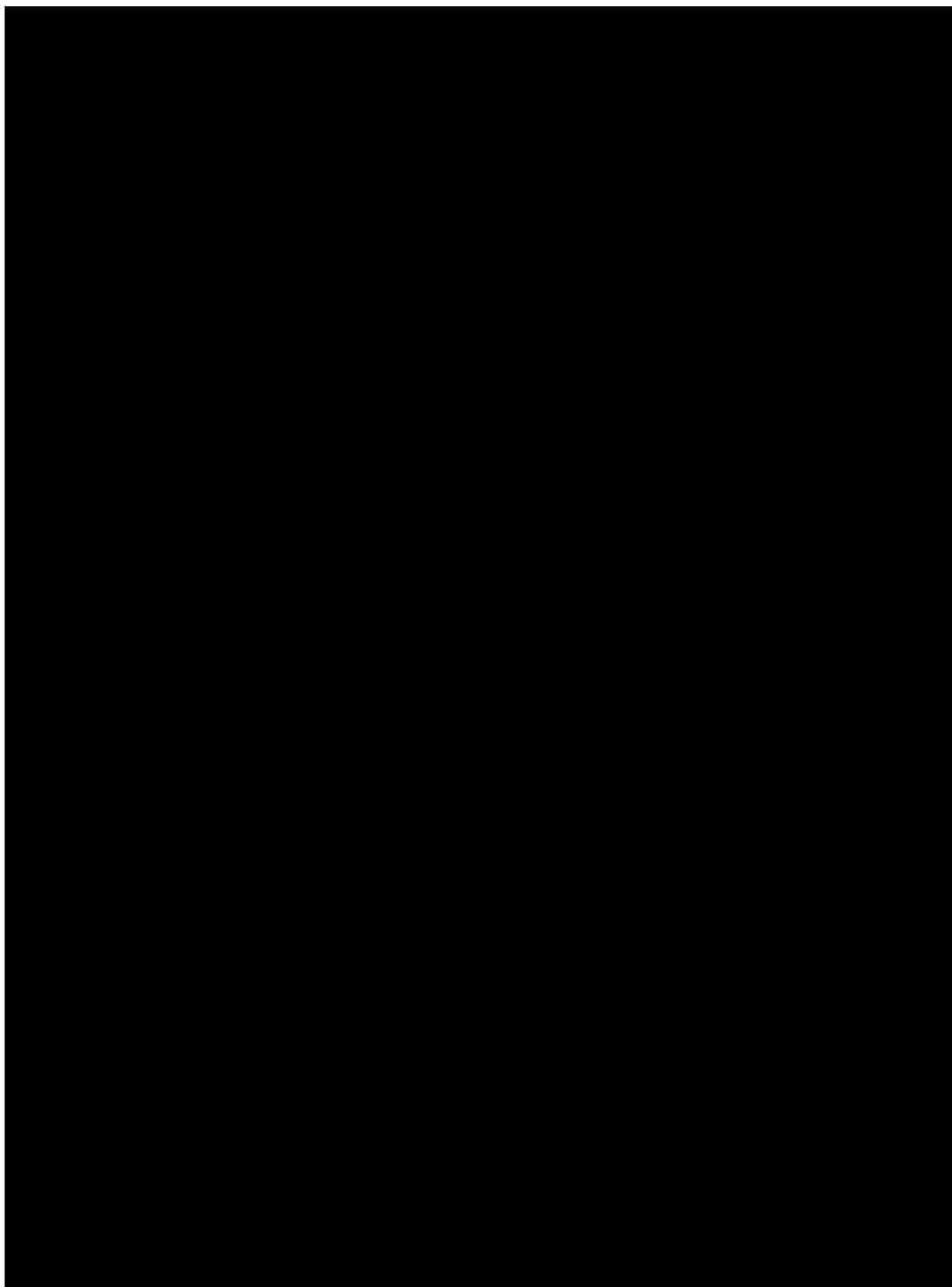
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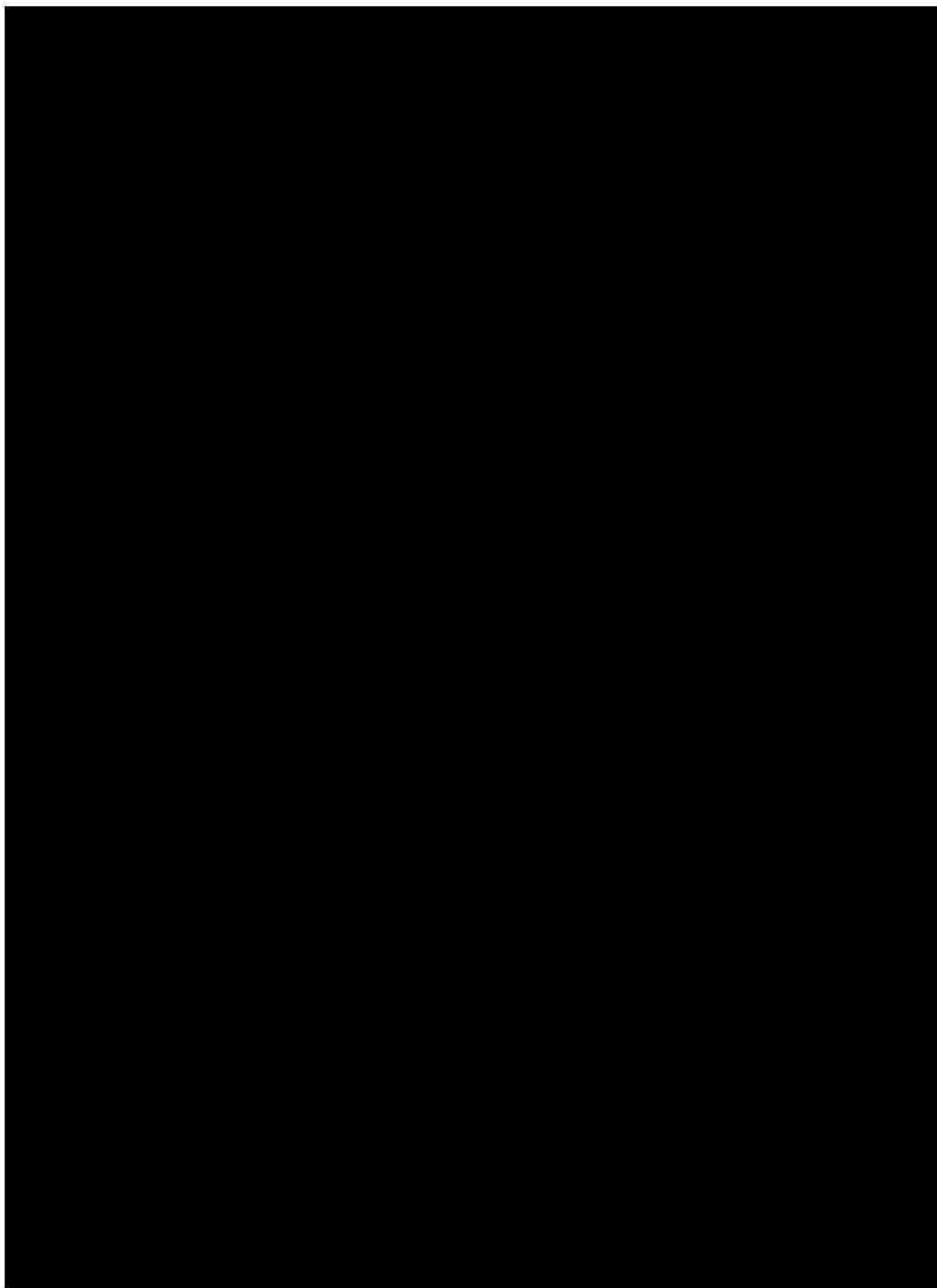
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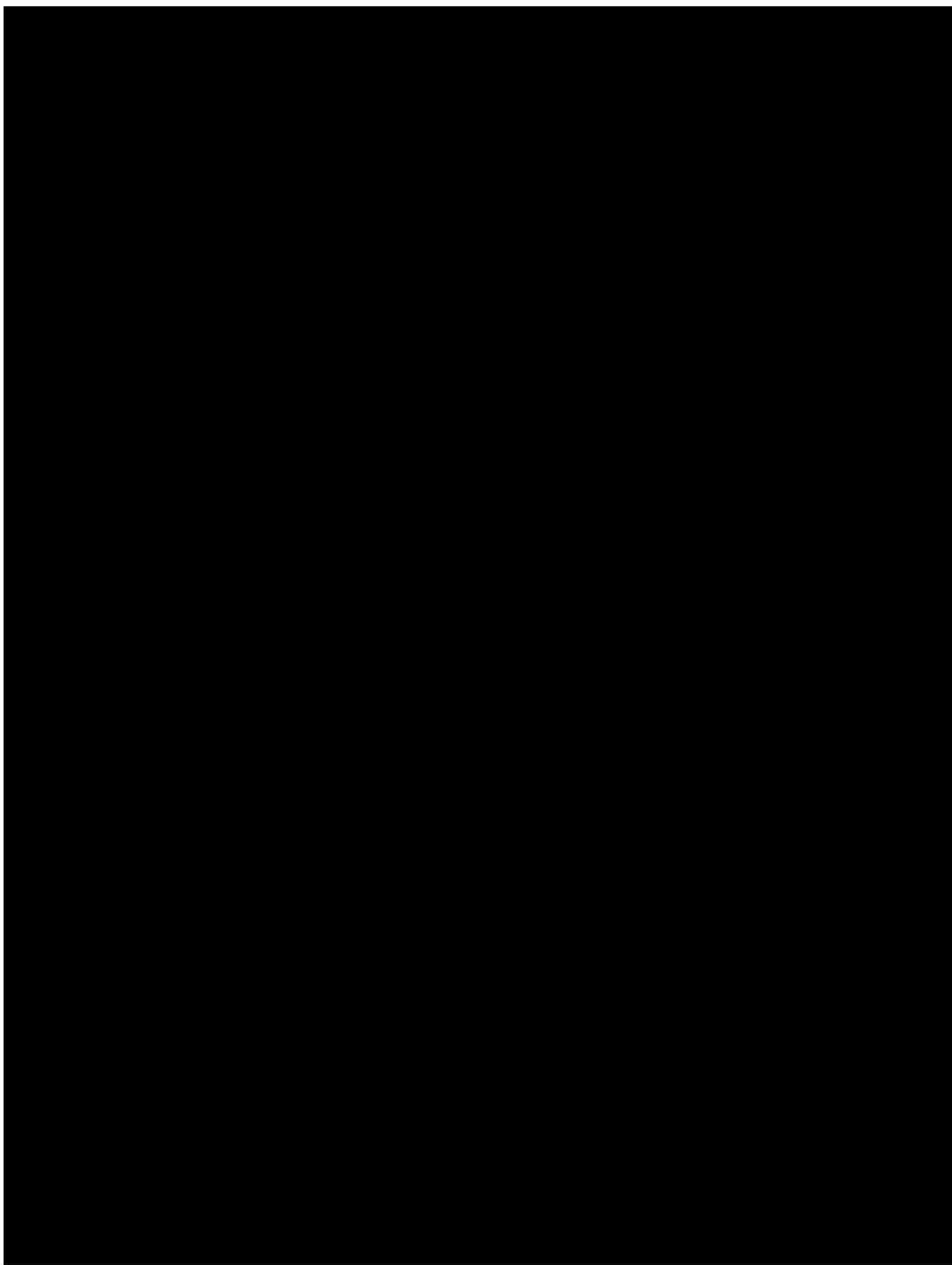
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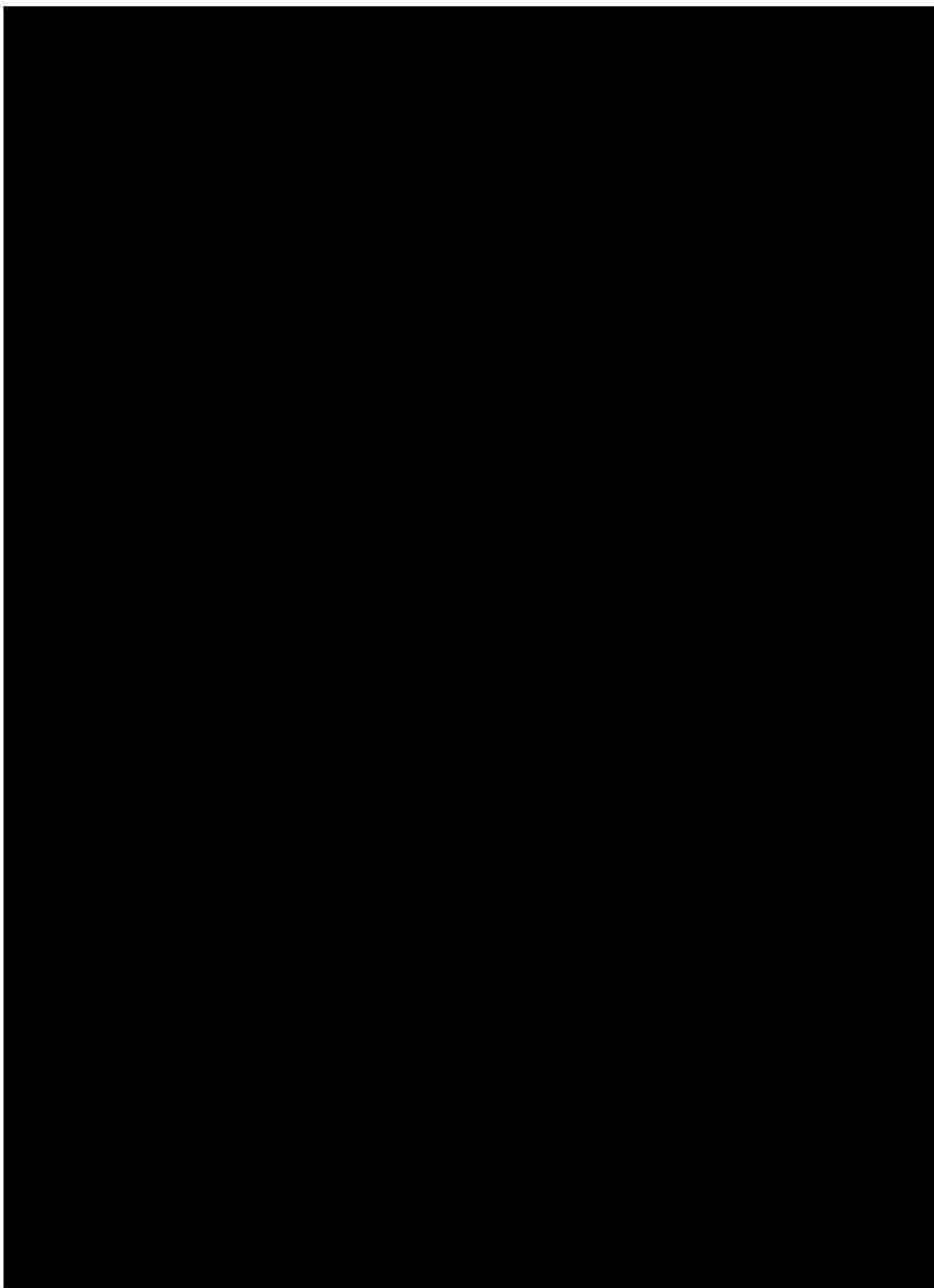
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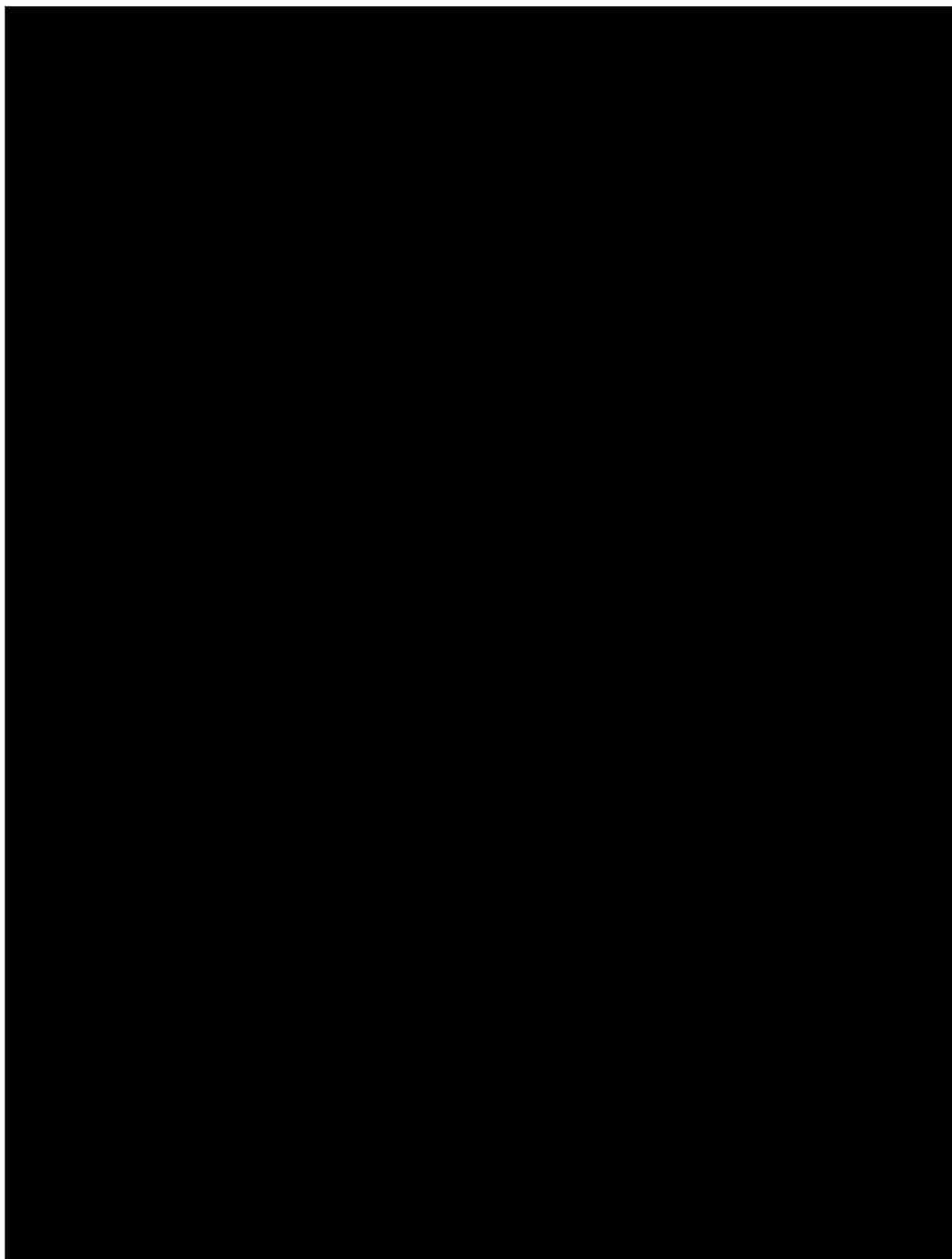
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