Periodic Benefit-Risk Evaluation Report

for

Active Substance: etranacogene dezaparvovec

ATC-Code: B02BD16

Medicinal Products Covered:

Invented Name of the Medicinal Product[a]	Marketing Authorisation Numbers	Date of Authorisation	Marketing Authorisation Holder[b]
Hemgenix	125772/0	22 November 2022	CSL Behring LLC

[a] Data for product in country of IBD
[b] First Marketing Authorisation Holder, full list available in Section 2

Authorisation Procedure in the EU: Centralised

International Birth Date (IBD): 22 November 2022

European Union Reference Date (EURD): 22 November 2022

Interval Covered by this Report:

22 November 2023 to 21 May 2024

Date of this Report:

22 July 2024

Marketing Authorisation Holder's Name and Address:

CSL Behring L.L.C.

[redacted]

Name and Contact Details of the QPPV:

[redacted]

Approved by (QPPV OR Delegate): [redacted]

Global Safety Lead

[redacted]

Executive Summary

Introduction:

This is the Periodic Benefit-Risk Evaluation Report (PBRER) for etranacogene dezaparvovec / CSL222 / Hemgenix. This PBRER summarises the safety data collected by the Marketing Authorisation Holder during the reporting period between 22 November 2023 up to and including the Data Lock Point of 21 May 2024. The PBRER is written in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E2C (R2) and the European Medicines Agency Good Pharmacovigilance Practices Module VII (Revision 1) guidance. The brand name for etranacogene dezaparvovec is Hemgenix.

Description of Product:

Etranacogene dezaparvovec (CSL222, Hemgenix) is a somatic gene therapy product that aims to deliver a nucleic acid expression cassette capable of driving expression and synthesis of functional Factor IX to the liver of patients with haemophilia B. One-time treatment with etranacogene dezaparvovec allows the patient to continuously produce functional human Factor IX Padua protein at levels which modify the severity of their haemophilia B disease.

[redacted]

Hemgenix is available as concentrate for solution for intravenous infusion.

Estimated Exposure:

Cumulatively, [redacted] subjects have been exposed to CSL222 (etranacogene dezaparvovec) in Marketing Authorisation Holder-sponsored clinical studies (completed and ongoing) since the Development International Birth Date of 20 August 2014.

[redacted]

Worldwide Marketing Authorisation Status:

Hemgenix was first authorised on 22 November 2022 in the [redacted] and is currently registered in [redacted]

Actions taken and proposed for safety reasons:

During the reporting period, no actions for safety reasons were taken for Hemgenix.

Benefit risk analysis:

Review of the data received during the reporting period of this PBRER did not change the current benefit-risk profile of Hemgenix for its authorised indications and populations. Overall, the data received is in line with previously known safety and efficacy data of Hemgenix.

Conclusions:

Based on the evaluation of information collected during this reporting period in context of the available cumulative data, no changes in the benefit-risk profile for Hemgenix have been observed. The overall benefit-risk balance for Hemgenix remains favourable. No changes to the Risk Management Plan are recommended.

The safety profile of Hemgenix is considered adequately reflected in the current Reference Safety Information and no safety amendments are warranted at present.

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List of Abbreviations

The following abbreviations are used in this Periodic Benefit-Risk Evaluation Report.

Abbreviation or Special Term	Definition
AAV(5)	Adeno-associated Virus (Serotype 5)
ABR	Annualised Bleeding Rate
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
aRMM	Additional Risk Minimisation Measures
AST	Aspartate aminotransferase
CCDS	Company Core Data Sheet
CSL222	CSL Behring's code for etranacogene dezaparvovec
DLP	Data Lock Point
DNA	Deoxyribonucleic acid
EU	European Union
FAS	Full Analysis Set
(h)FIX	(Human) Factor IX
GB	Great Britain
HCP	Health Care Professional
ICSR	Individual Case Safety Report
IV	Intravenous
MAH	Marketing Authorisation Holder
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralising Antibody
PBRER	Periodic Benefit-Risk Evaluation Report
PT	Preferred Term
PWH	Person with Haemophilia
RMP	Risk Management Plan
RSI	Reference Safety Information
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics

Abbreviation or Special Term	Definition
SMQ	Standardised MedDRA Query
US	United States

1 Introduction

This is the 3rd Periodic Benefit-Risk Evaluation Report (PBRER) for Hemgenix (etranacogene dezaparvovec, CSL222). This PBRER summarises the safety data collected by the Marketing Authorisation Holder (MAH) covering the period between 22 November 2023 up to and including the Data Lock Point (DLP) of 21 May 2024. This PBRER is written in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E2C (R2) and the European Medicines Agency Good Pharmacovigilance Practices Module VII (Revision 1) guidelines. The International Birth Date for Hemgenix is 22 November 2022 in the [redacted] The brand name for etranacogene dezaparvovec is Hemgenix.

Etranacogene dezaparvovec / CSL222 / Hemgenix will be referred to throughout the document as Hemgenix, when used for information from post-marketing sources, and / or CSL222, when used for information from clinical development.

Hemgenix / CSL222 is a somatic gene therapy product designed to deliver a nucleic acid expression cassette capable of driving expression and synthesis of functional Factor IX (FIX) to the liver of patients with haemophilia B. One-time treatment with Hemgenix allows the patient to continuously produce functional human Factor IX (hFIX) Padua protein at levels and aims to establish sustained FIX activity, thereby protecting against bleeding without burdensome FIX replacement. Hemgenix consists of a codon-optimised coding Deoxyribonucleic acid (DNA) sequence of the gain-of-function Padua variant of the human FIX (hFIXco-Padua), under control of the liver-specific LP1 promoter, encapsulated in a non-replicating recombinant adeno-associated viral vector of serotype 5 (AAV5).

Following single intravenous infusion (IV), Hemgenix preferentially targets liver cells, where the vector DNA resides almost exclusively in episomal form. After transduction, Hemgenix directs long-term liver-specific expression of Factor IX-Padua protein. As a result, it partially or completely ameliorates the deficiency of circulating FIX procoagulant activity in patients with Haemophilia B.

The approved indication for Hemgenix in the [redacted] is the treatment of severe and moderately severe Haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors.

The approved indication for Hemgenix in the [redacted] is the treatment of adults with haemophilia B (congenital Factor IX deficiency) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes.

The indications in [redacted] are presented in [redacted].

Hemgenix is available as concentrate for solution for intravenous infusion. Information regarding the recommended dose can be found in the Reference Safety Information (RSI) presented in [redacted]

2 Worldwide Marketing Authorisation Status

Hemgenix was first authorised on 22 November 2022 in [redacted]

[redacted]

During the reporting period, Hemgenix was approved [redacted]

A detailed overview of the current worldwide registration status and the approved indications for Hemgenix can be found in [redacted]

3 Actions Taken in the Reporting Interval for Safety Reasons

During the reporting period, no actions for safety reasons were taken by the MAH, sponsors of clinical studies, regulatory authorities, data monitoring committees or ethics committees.

4 Changes to Reference Safety Information

The RSI in effect at the start of the reporting period was the Company Core Safety Information included in the CCDS, [redacted]

During the reporting period, no changes were made to the RSI. A copy of the RSI in effect at the start and end of the reporting period can be found in [redacted]

5 Estimated Exposure and Use Patterns

5.1 Cumulative Subject Exposure in Clinical Studies

Up to the DLP of this PBRER, [redacted] subjects have been enrolled into the CSL222 clinical programme, of which [redacted] subjects have been treated with CSL222.

Summaries of the estimated cumulative subject exposure are presented in Table 5-1, Table 5-2, and Table 5-3.

Table 5-1: Cumulative Subject Exposure

Treatment	Number of Subjects
Completed Studies	
[redacted]	[redacted]
Ongoing Studies [a]	
[redacted]	[redacted]
Completed and Ongoing Studies	
CSL222	[redacted]

[a] Subjects were treated in the [redacted] studies only. Seven subjects consented to participate in the [redacted] studies without an exposure to CSL222 until 21 May 2024, no subject consented to participate in study [redacted] until the DLP.
[b] All 3 subjects who participated in Study [redacted] consented to participate in study [redacted] all subjects of Study [redacted] are expected to be enrolled into the [redacted] study (see Section 7.3). There will be no treatment with CSL222 in clinical study [redacted].

Table 5-2: Cumulative Subject Exposure to CSL222 from Ongoing and Completed Clinical Studies ([redacted]) by Age and Gender[a]

	Number of Subjects		
Age Range[b]	**Male**	**Female**	**Total**
Adults (18 to 64 years)	[redacted]	[redacted]	[redacted]
Elderly (> 65 years)	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

[a] Data from ongoing and completed studies as of 21 May 2024.
[b] Age of the subjects at the time of informed consent.

Table 5-3: Cumulative Subject Exposure to CSL222 from Ongoing and Completed Clinical Studies ([redacted] by Ethnic Origin[a]

Ethnic Origin	Number of Subjects
Asian	[redacted]
Black or African American	
White	
Other	
Unknown	
Total	

[a] Data from ongoing and completed studies as of 21 May 2024.

5.2 Cumulative and Interval Patient Exposure from Marketing Experience

5.2.1 Post-authorisation (Nonclinical Study) Exposure

Cumulatively, [redacted] patients have been treated with Hemgenix in the post-marketing setting (all [redacted] of them in the current reporting period.

Cumulative and interval sales volume is presented in Table 5-4.

Table 5-4: Patients treated with Hemgenix in the post-marketing setting

Previous Period 22 May 2023 to 21 Nov 2023	Current Period 22 Nov 2023 to 21 May 2024	Cumulatively 22 May 2023 to 21 May 2024
[redacted]	[redacted]	[redacted]

5.2.2 Post-authorisation Use in Special Populations

No information on post-authorisation use in special populations is available. There were no noninterventional studies or registries designed to obtain information on use in special populations and no other information was collected on use in special populations.

5.2.3 Other Post-authorisation Use

No information on other post-authorisation use considered relevant to the evaluation of safety and / or benefit-risk has been identified during the reporting period.

6 Data in Summary Tabulations

The data in the summary tabulations appended to this report are based on the individual case safety reports (ICSRs) that have been received by the MAH at the time of DLP and meet the 4 minimal criteria of a valid case, as specified in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E2D guideline. The adverse drug reaction (ADR) / adverse event (AE) terms in the summary tabulations are arranged by internationally agreed order by primary System Organ Class and alphabetically by Preferred Term (PT). A single ICSR can include more than one event. Therefore, the total number of events may be greater than the total number of case reports presented.

6.1 Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA), version 27.0 has been used for the presentation and analysis of AEs in this report.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

A cumulative summary tabulation of all serious adverse events (SAEs) from all MAH-sponsored clinical studies since the Development International Birth Date is presented in [redacted]

Note: The cumulative summary tabulation of SAEs will only have studies listed if at least one SAE was reported in the study. Studies with no SAEs will not be listed.

6.3 Cumulative and Interval Summary Tabulations from Post-marketing Data Sources

Cumulative and interval summary tabulations of all spontaneous ICSRs and serious ADRs derived from noninterventional studies and other solicited sources for Hemgenix are listed in [redacted]

An overview of the interval and cumulative ADR data is presented in Table 6-1.

Table 6-1: Overview of ADR Data

[redacted]

7 Summaries of Significant Findings from Clinical Studies During the Reporting Interval

Safety and efficacy concerns obtained during the reporting period of this PBRER from information from MAH-sponsored interventional studies are presented in this section.

No MAH-sponsored interventional studies with the primary aim of identifying, characterising, or quantifying a safety hazard are conducted, the [redacted] and [redacted] interventional clinical studies are intended to investigate the efficacy and safety profile of CSL222 (see Section 7.2 and [redacted].

7.1 Completed Clinical Studies

During the reporting period, one study with CSL222 was completed ([redacted] study). No new clinically important efficacy and safety findings have arisen from this clinical study.

The following table presents a summary of the efficacy and safety findings:

Study Title: Phase IIb, open-label, single-dose, single-arm, multi-centre trial to confirm the Factor IX activity level of the serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimised human factor IX gene (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately severe hemophilia B

Number of subjects enrolled	[redacted]
Subject demographics	[redacted] Age: [redacted] at screening
Treatment arms and ratio	Not applicable
Investigational Medicinal Product	Subjects received a single IV infusion [redacted] CSL222
Duration of subject participation	5 years
Efficacy results	[redacted]

Safety results	[redacted]
Conclusion	Overall, CSL222 has a favourable benefit-risk balance for adults with severe or moderately severe haemophilia B. Results from Study [redacted] demonstrate that CSL222 is safe and efficacious for the treatment of severe or moderately severe haemophilia B.

ALT = alanine aminotransferase; FIX = factor IX; IV = intravenous; SAE = serious adverse event; TEAE = treatment-emergent adverse event

There were no emergent safety signals reported and subjects maintained stable and measurable mean FIX activity levels at 50%, with all 3 subjects remaining free of FIX prophylaxis.

7.2 Ongoing Clinical Studies

[redacted]

[redacted]

7.3 Long-term Follow-up

[redacted]

[redacted]

7.4 Other Therapeutic Use of Medicinal Product

No other programs following a specific protocol with solicited reporting for Hemgenix / CSL222 were ongoing or were completed during the reporting period.

7.5 New Safety Data Related to Fixed Combination Therapies

Hemgenix / CSL222 is not authorised or under development as a component of a fixed dose combination product or a multidrug regimen.

8 Findings from Noninterventional Studies

[redacted]

9 Information from Other Clinical Studies and Sources

9.1 Other Clinical Studies

The MAH is not aware of any other clinical studies with CSL222, that were conducted during the reporting period of this PBRER.

9.2 Medication Errors

The relevant information on patterns of medication errors was obtained by searching the MAH's Global Safety Database for all cases containing at least one PT pertaining to the Medication errors (Standardised MedDRA Query [SMQ]) (Narrow).

During the reporting period, no reports of medication errors were received by the MAH.

10 Nonclinical Data

[redacted]

11 Literature

A standardised search in the scientific literature databases MEDLINE and EMBASE was performed for articles relevant to Hemgenix / CSL222, covering the reporting period. In addition, unpublished manuscripts when made available have been reviewed to identify new and significant safety findings. The retrieved abstracts and / or full texts were reviewed for important safety findings. Adverse reactions deriving from published individual case reports are included in the summary tabulations in [redacted]

The review of the published and unpublished literature retrieved during the reporting period did not yield any significant safety findings for Hemgenix / CSL222.

12 Other Periodic Reports

The MAH prepares only a single PBRER for Hemgenix / CSL222 that covers all indications. The MAH is not aware of any PBRERs prepared by other parties during the reporting period.

13 Lack of Efficacy in Controlled Clinical Studies

As presented in Section 7, controlled clinical studies with CSL222 were conducted during the reporting period. No new data indicating lack of efficacy, or lack of efficacy relative to established therapies that could reflect a significant risk to the treated population were identified in the reporting period.

14 Late-breaking Information

[redacted]

15 Overview of Signals: New, Ongoing or Closed

15.1 Signals

During the reporting period, no signal evaluation was ongoing or completed for Hemgenix / CSL222.

15.2 Monitored Topics

During the reporting period, there were no requests from Health Authorities for the monitoring of specific topics for Hemgenix / CSL222.

16 Signal and Risk Evaluation

16.1 Summary of Safety Concerns

The summary of the important safety concerns in effect at the start of the reporting period of this PBRER is presented in Table 16-1. The summary is derived from the safety specification described in the EU-Risk Management Plan (RMP), version 1.0, dated 14 December 2022.

The EU-RMP version 1.0, is the reference RMP for this PBRER, and only safety concerns included in this RMP are presented and evaluated in this PBRER.

Table 16-1: Summary of Important Safety Concerns at the Start of the Reporting Period

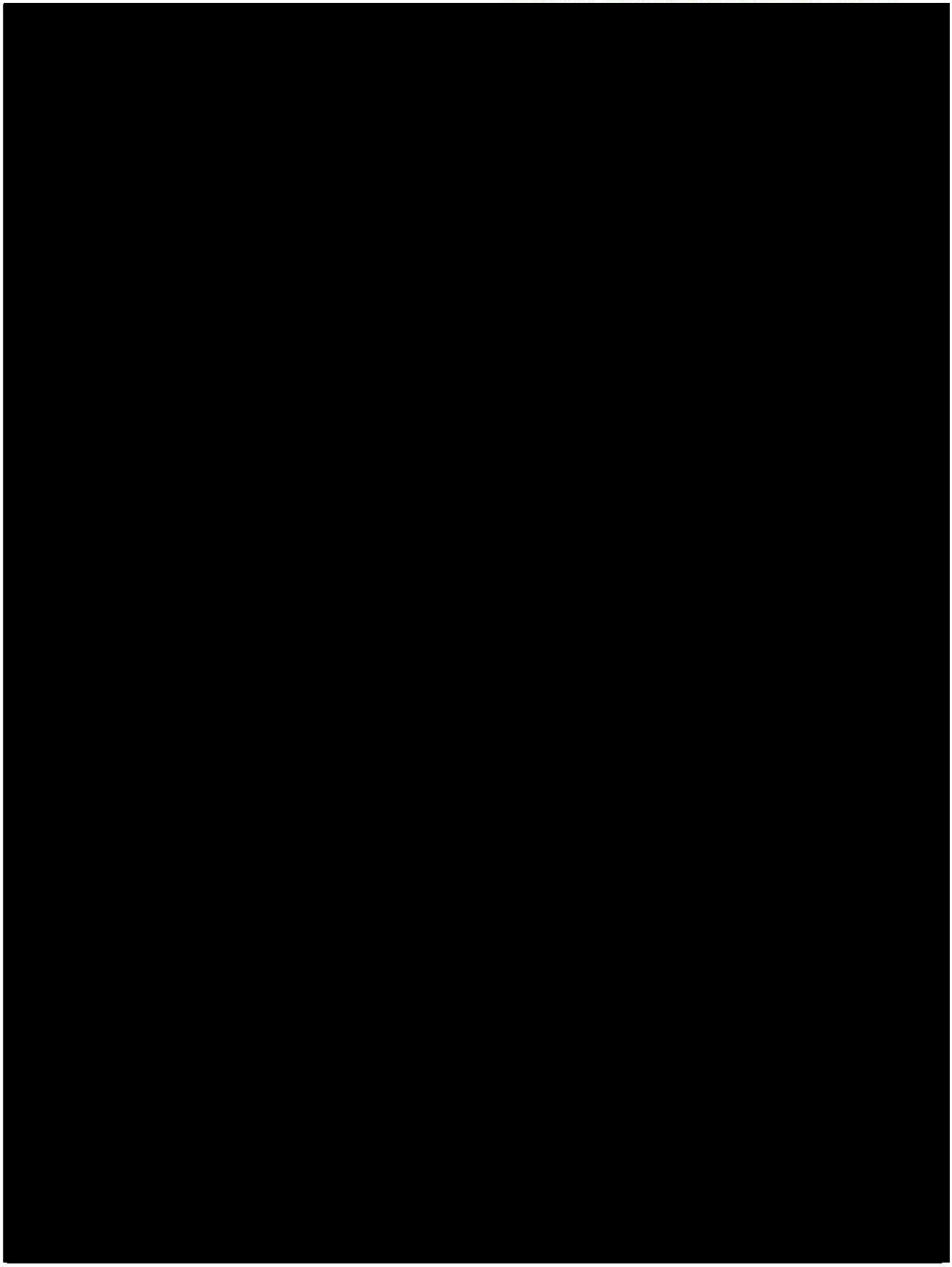
[redacted]

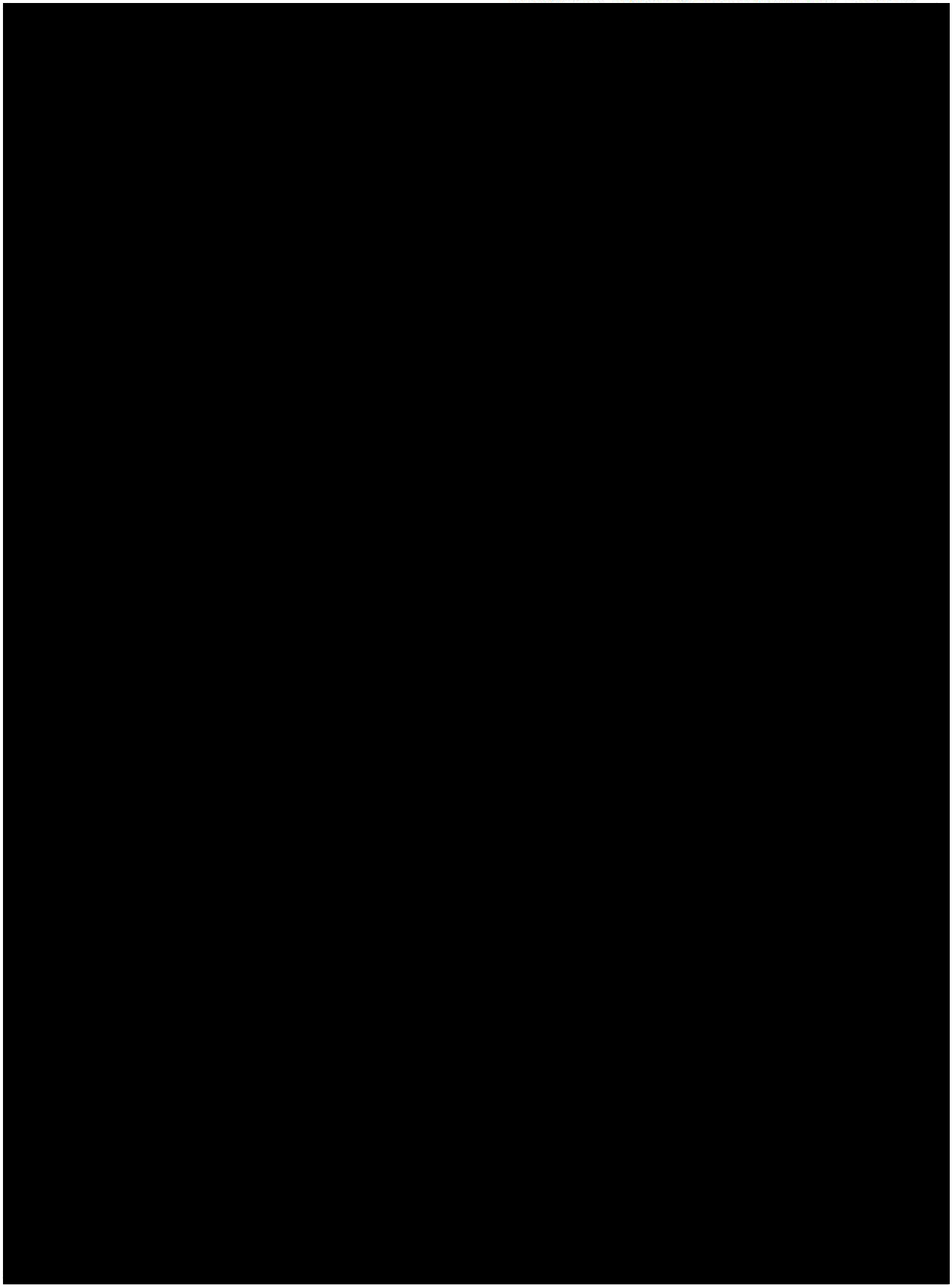
16.2 Signal Evaluation

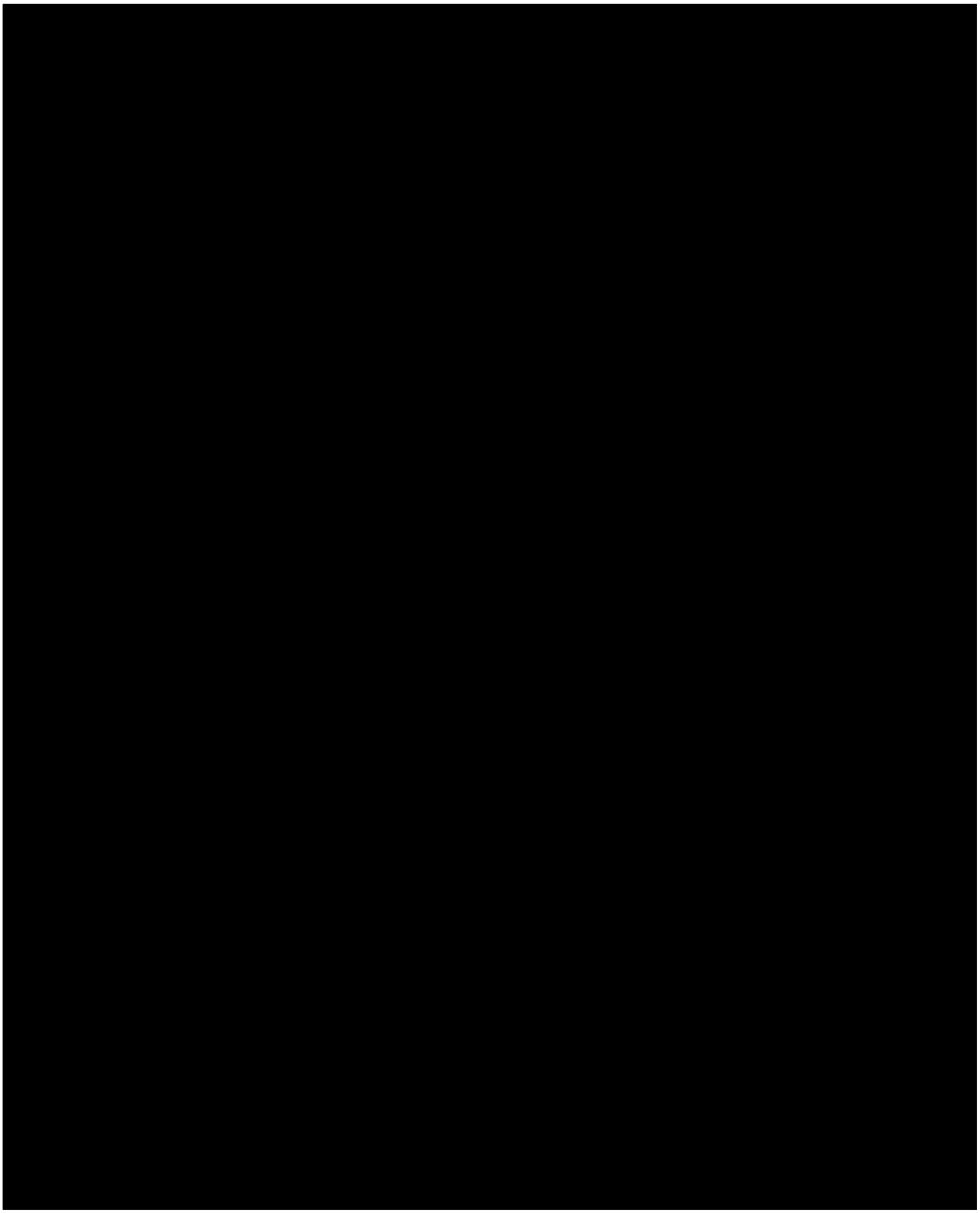
During the reporting period no signal evaluations were ongoing, refuted or closed.

16.3 Evaluation of Risks and New Information

[redacted]



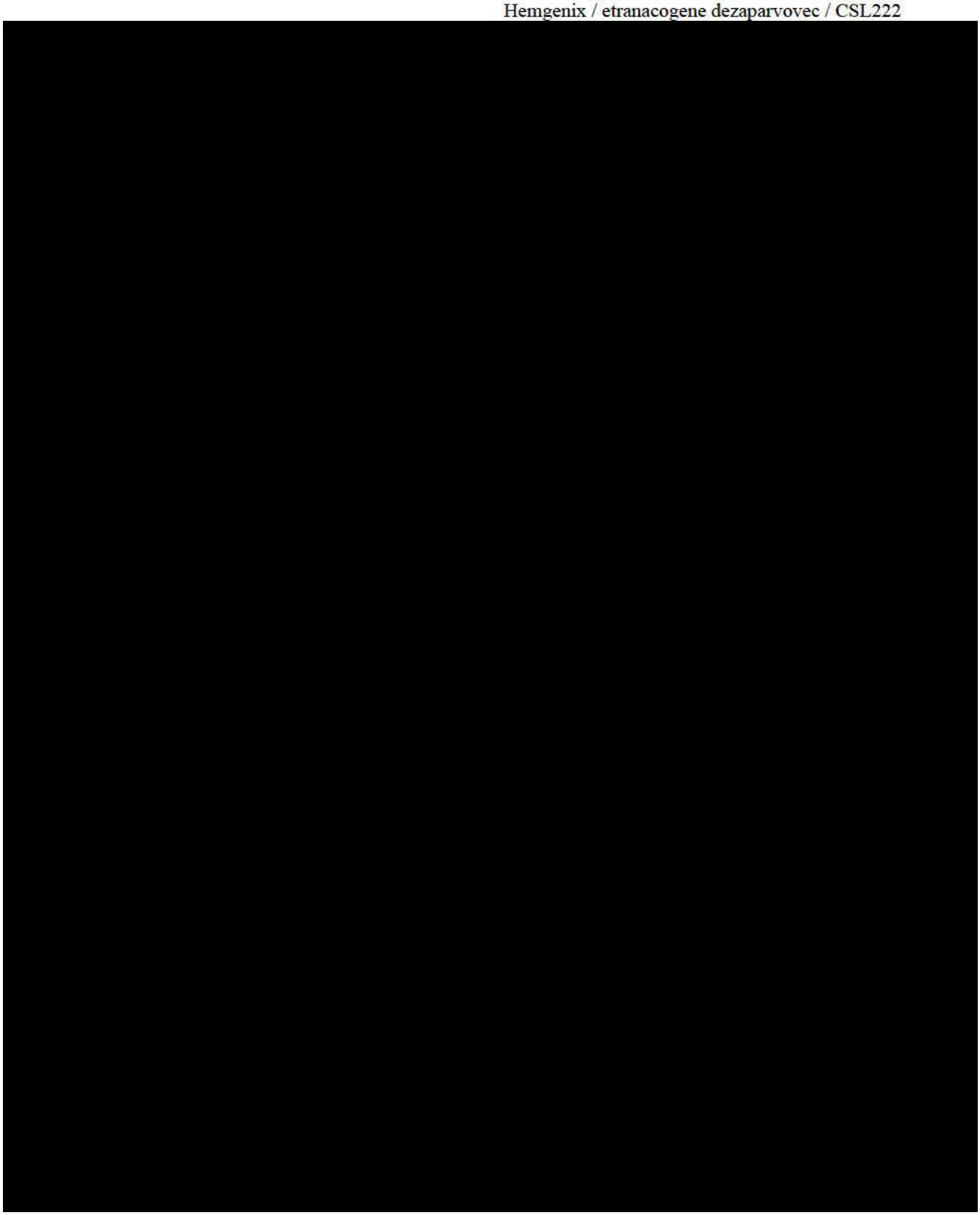


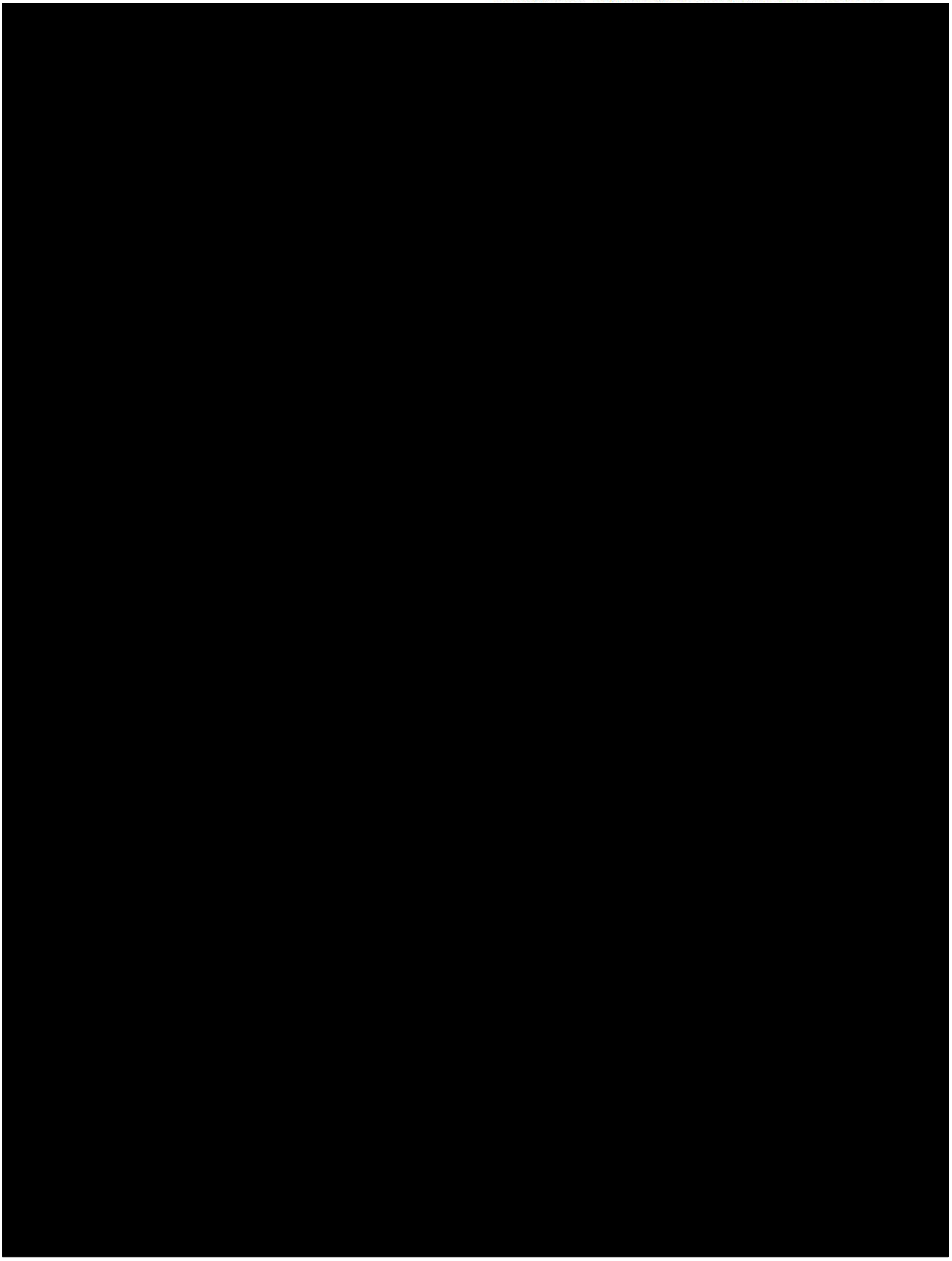


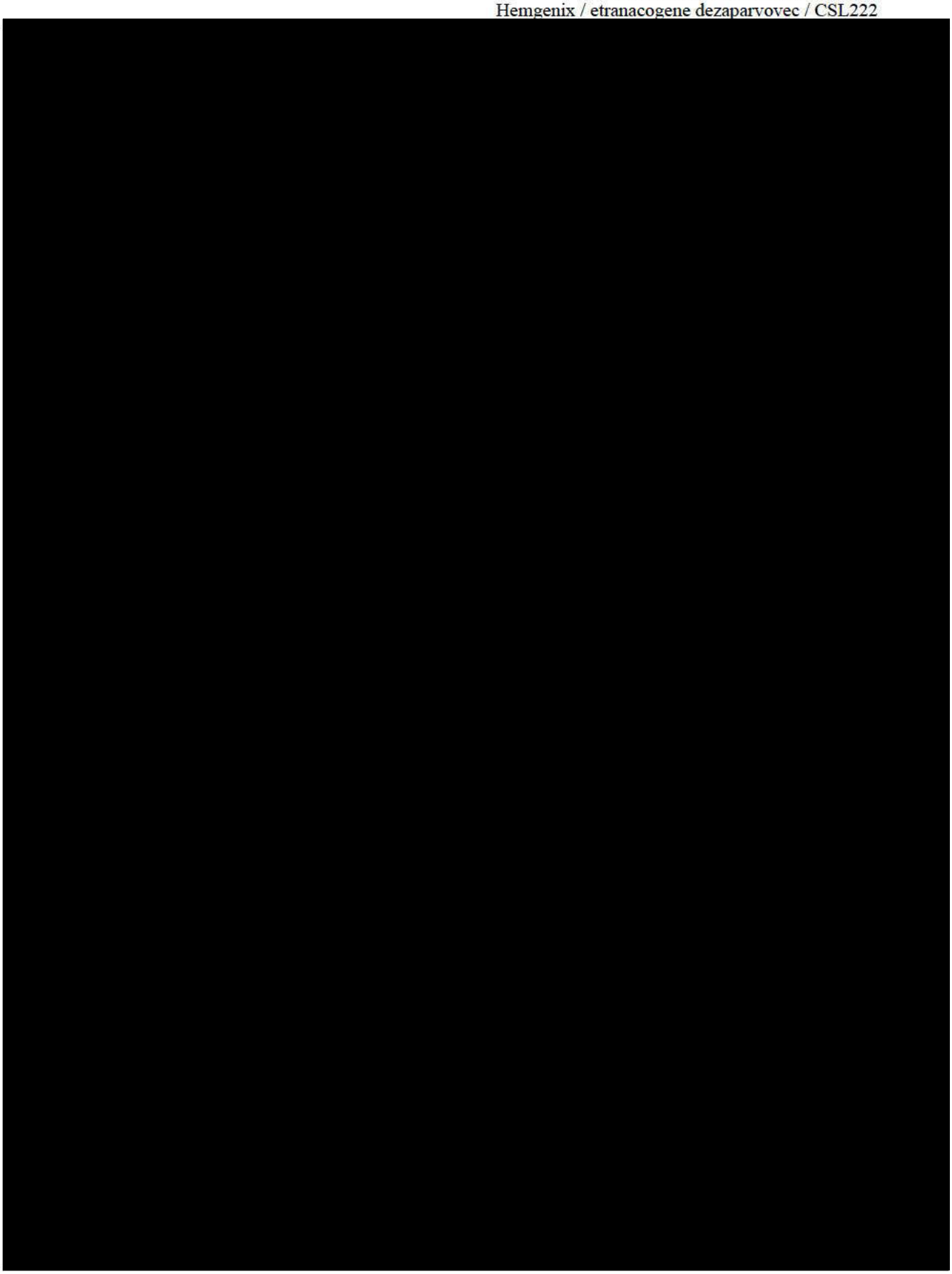
[redacted]

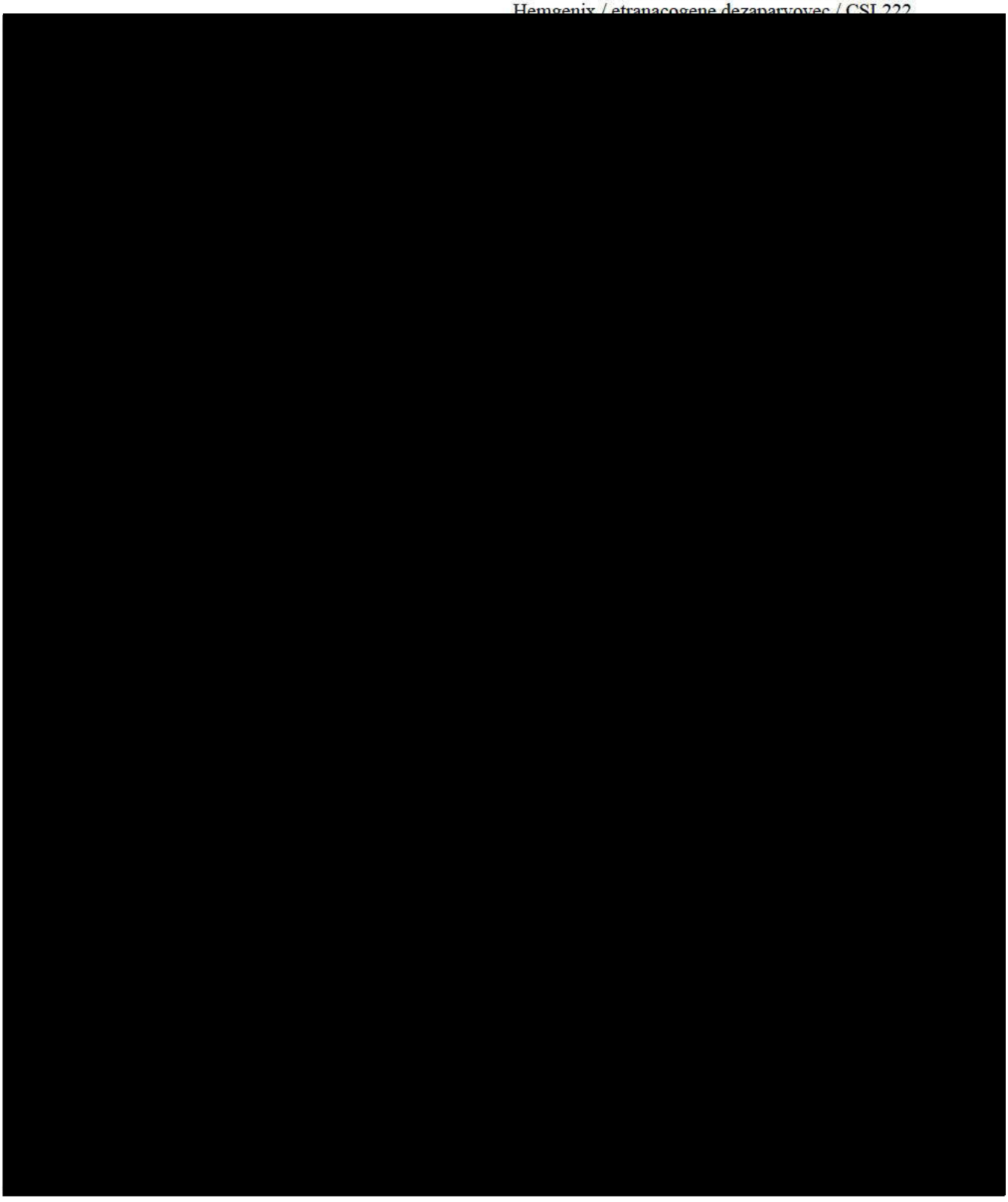
16.4 Characterisation of Risks

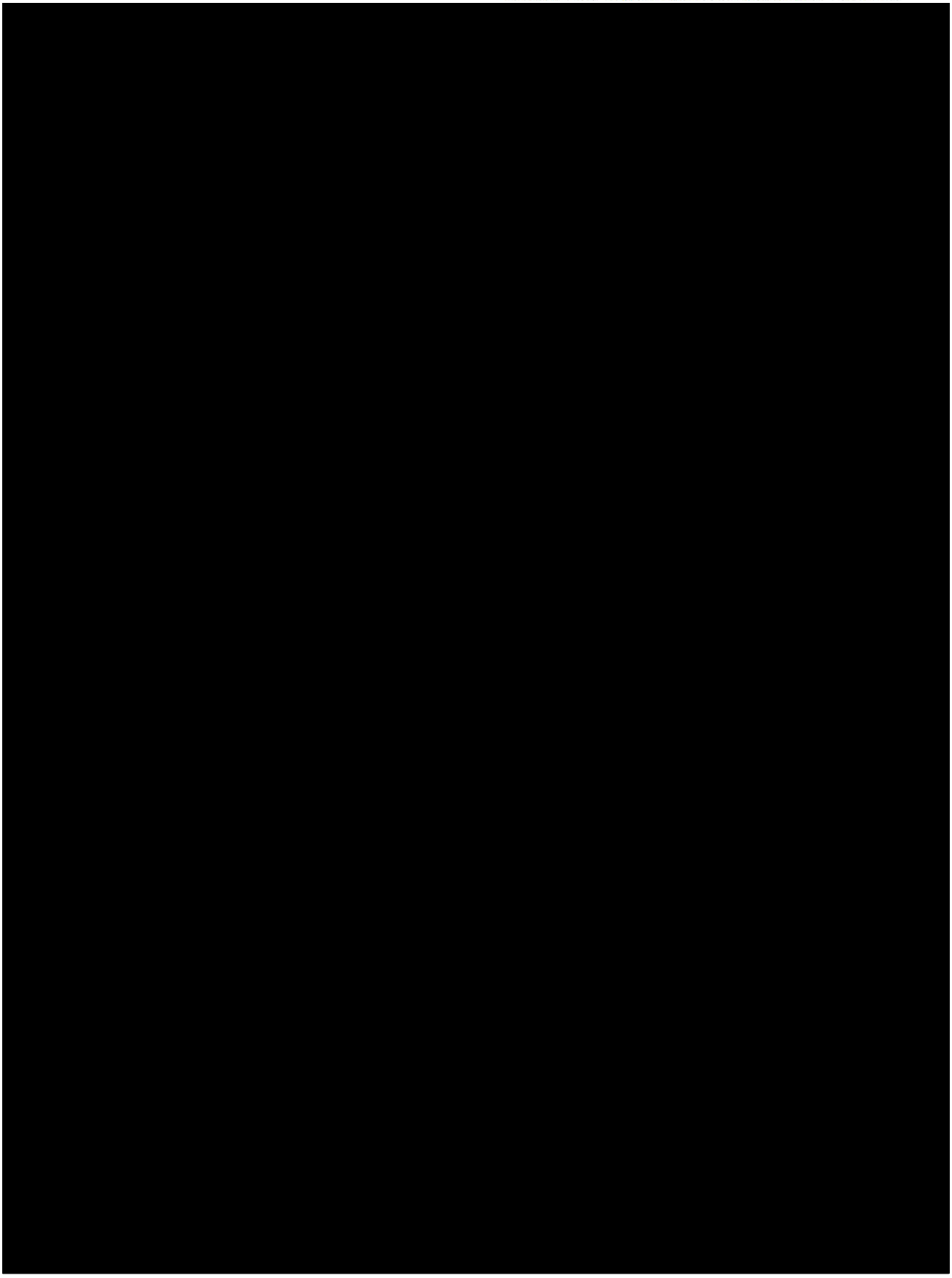
[redacted]

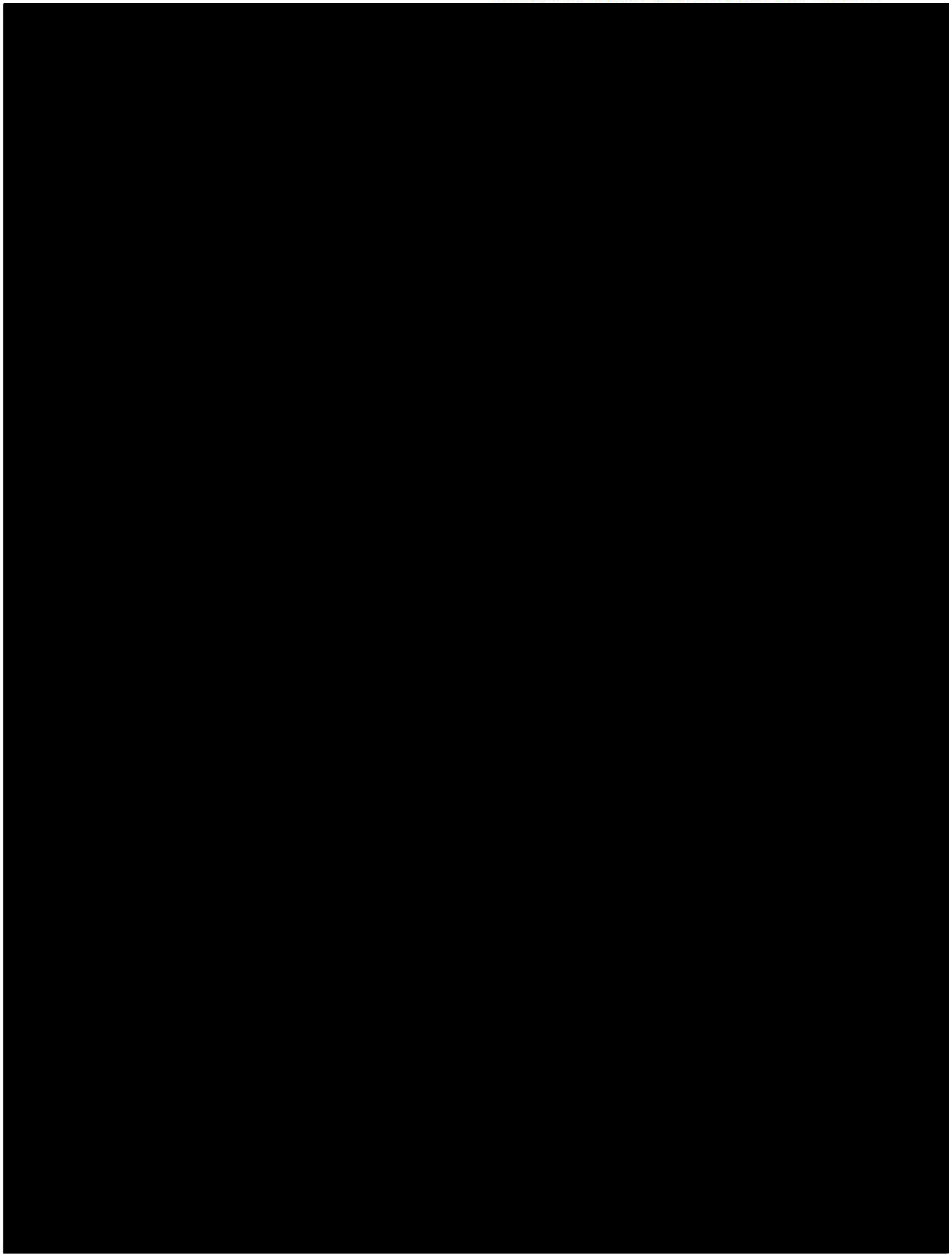


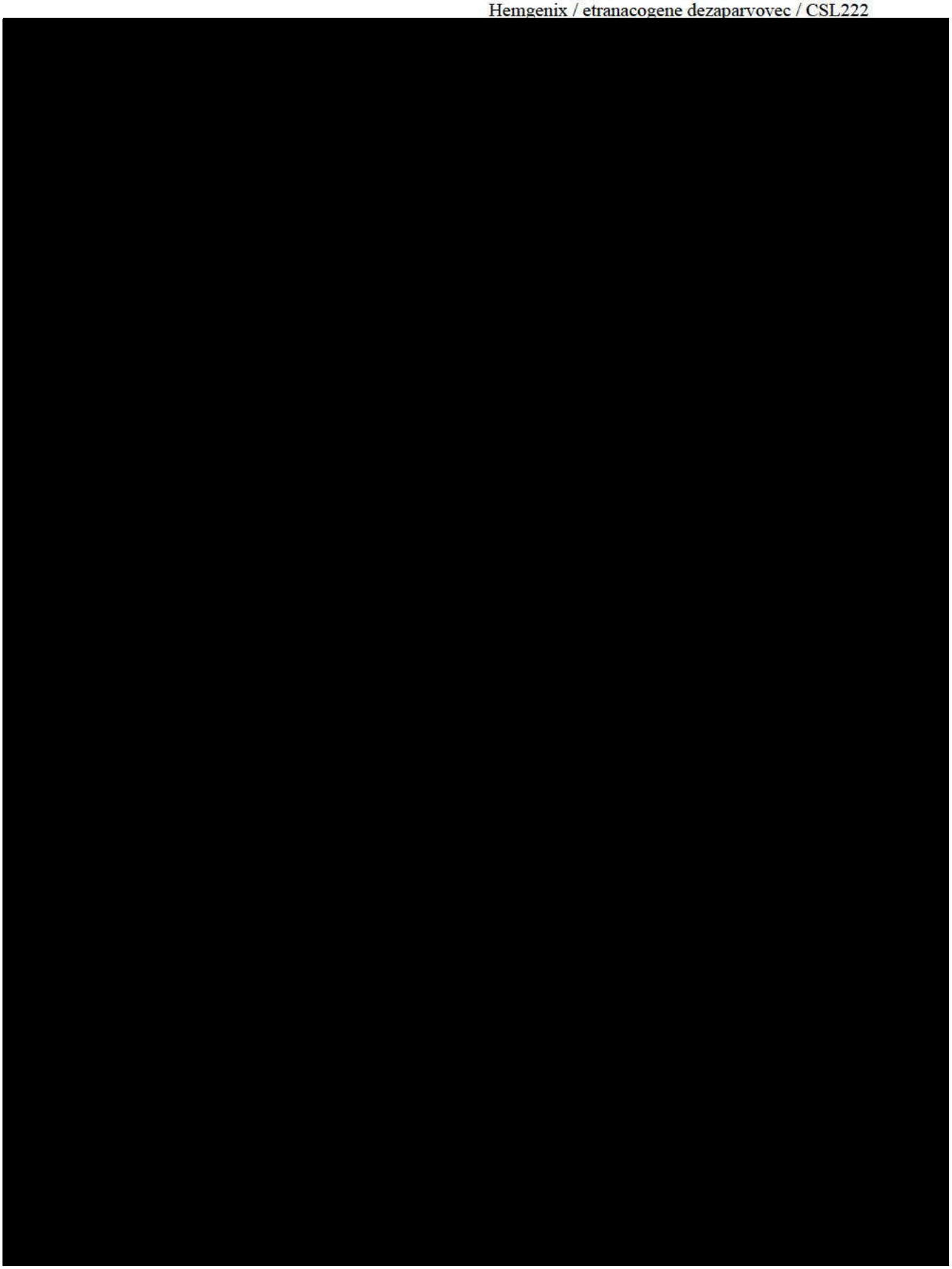


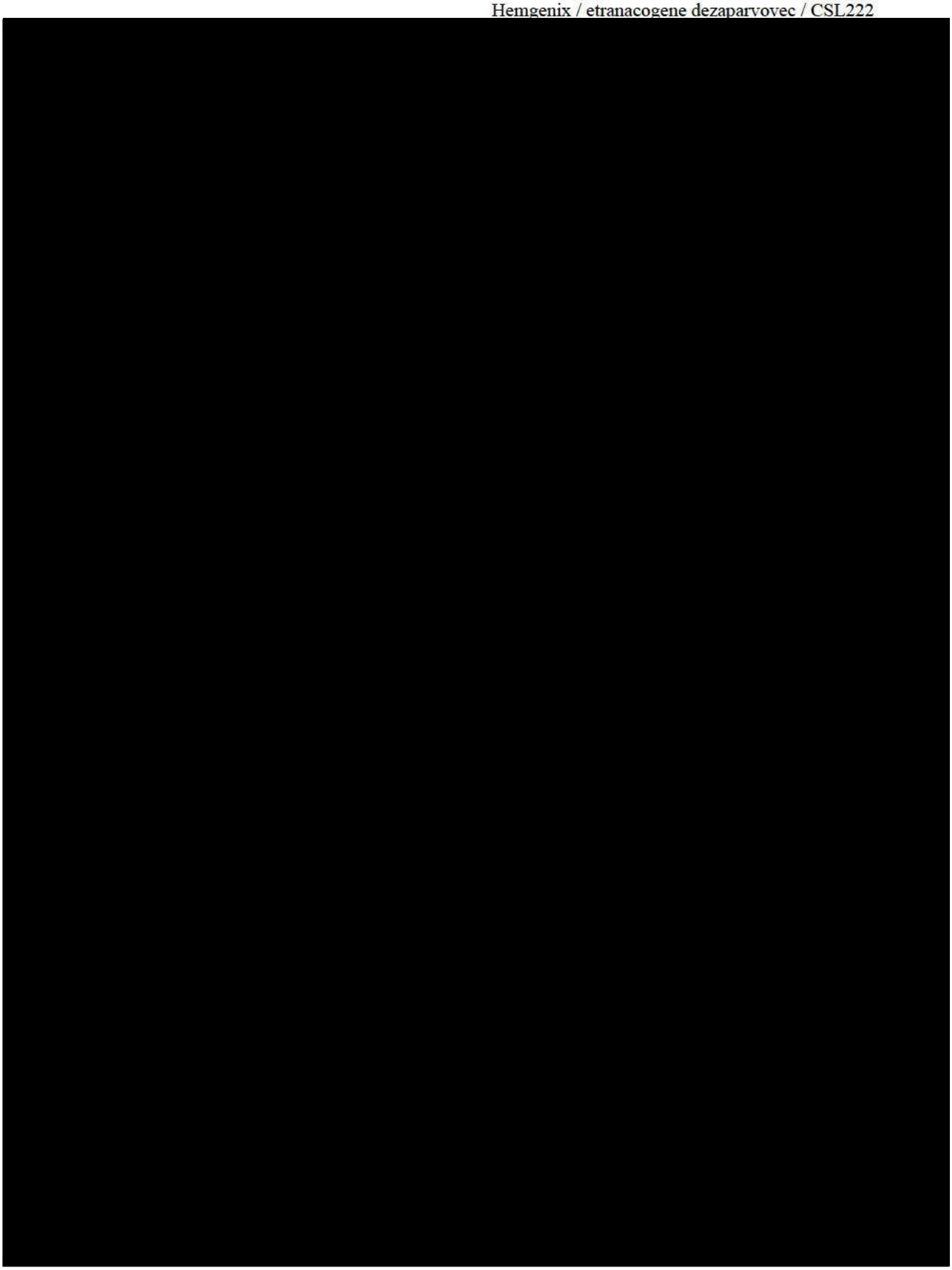


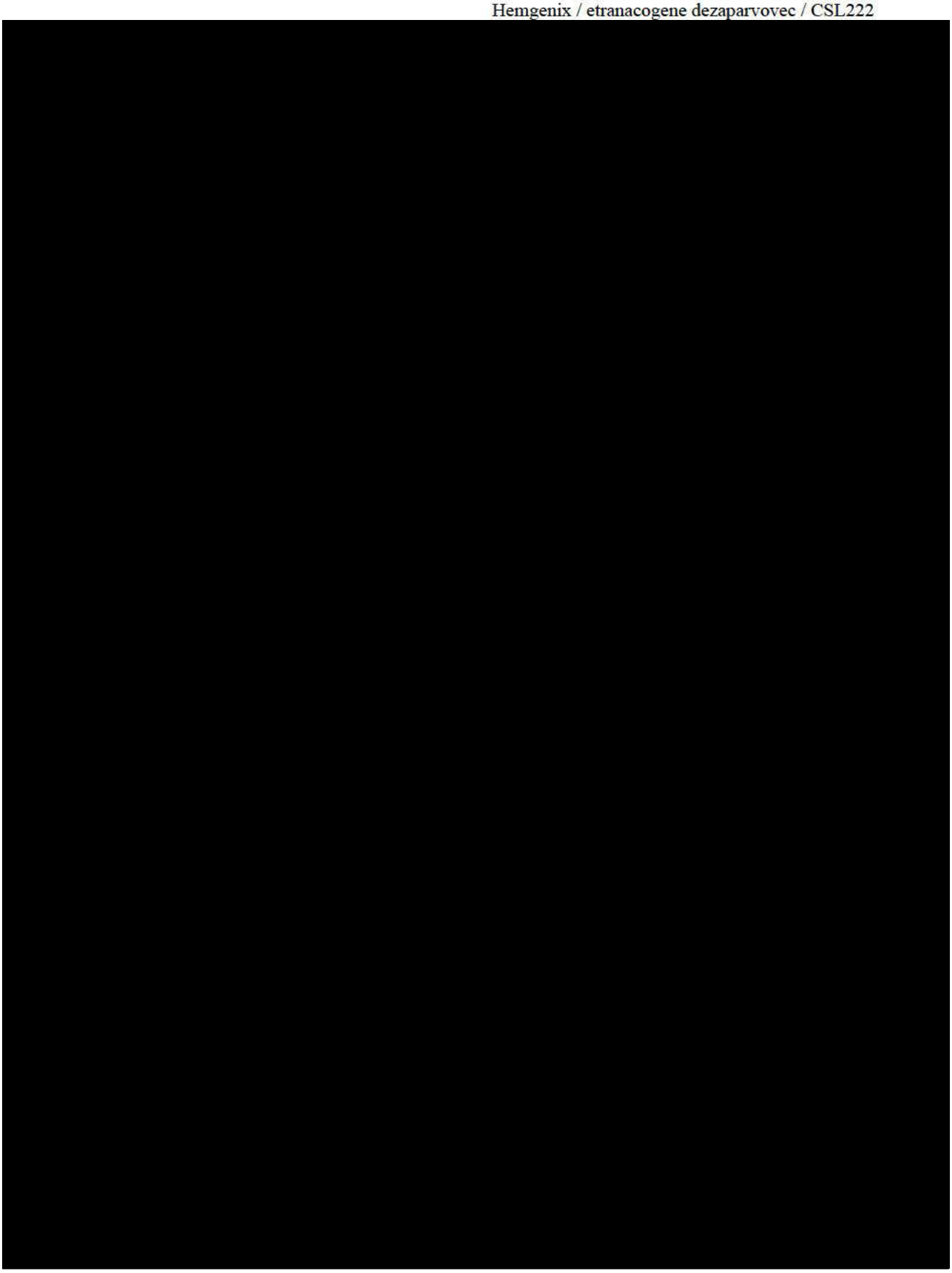


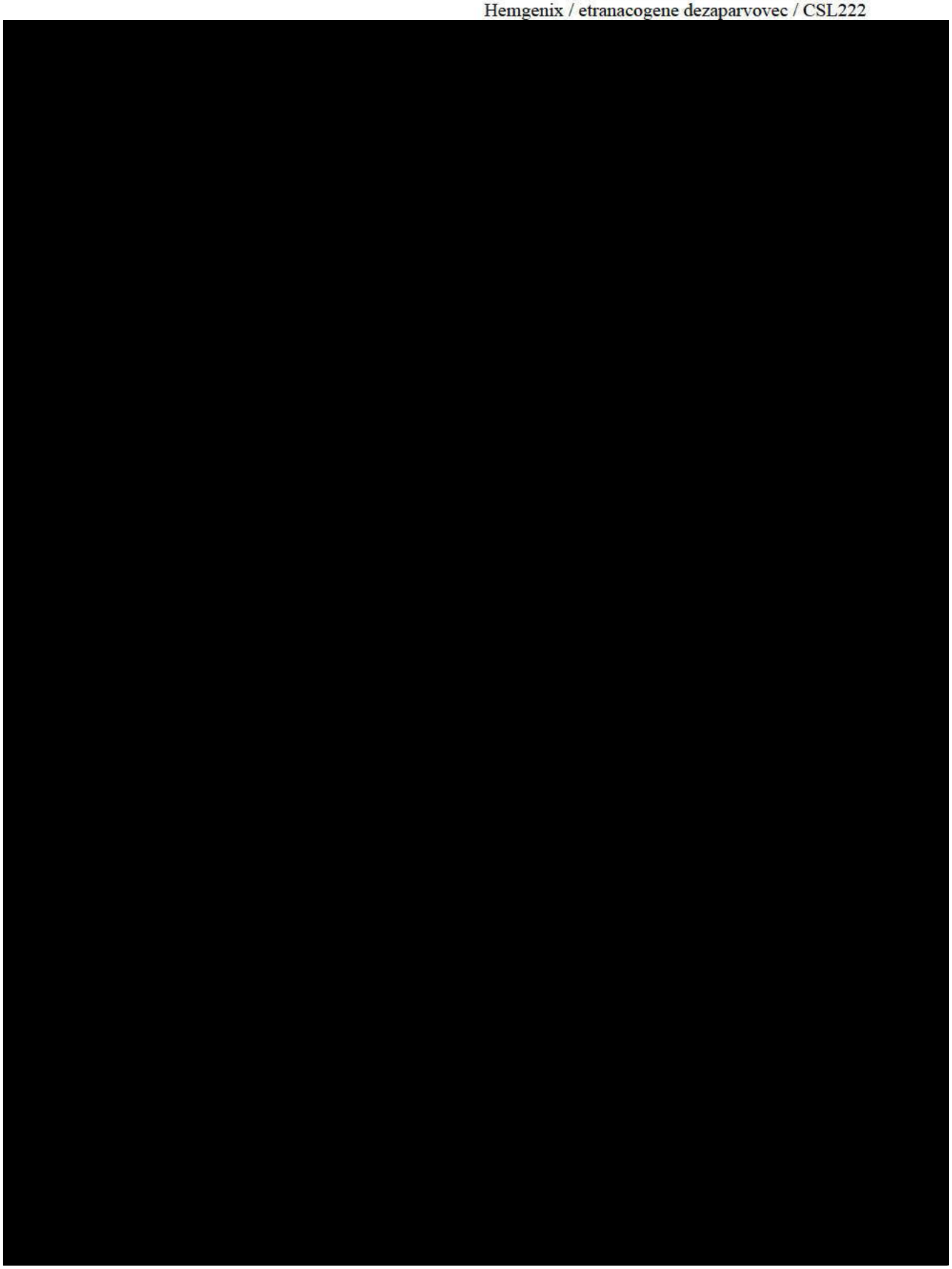


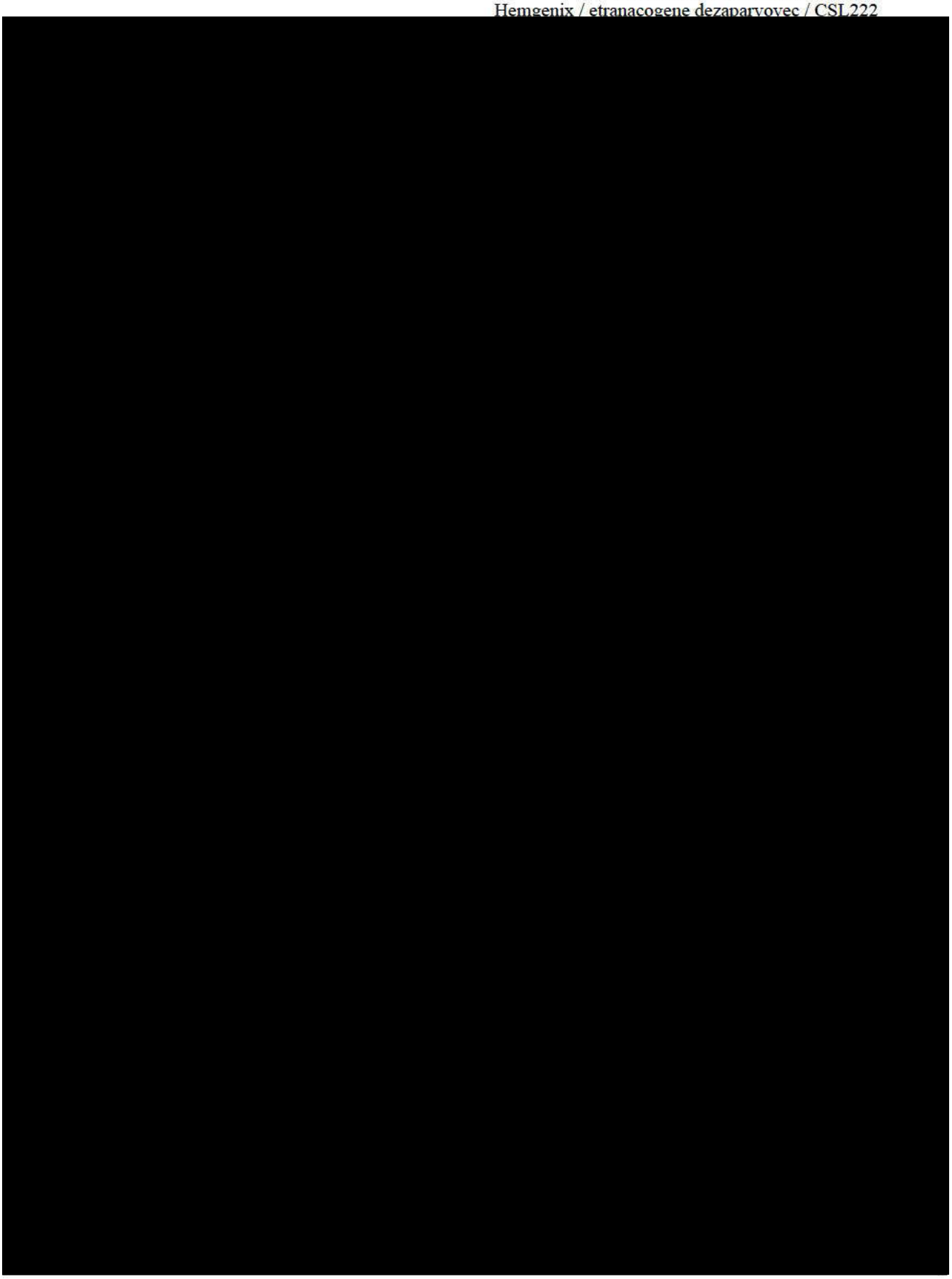












[redacted]

[redacted]

16.5 Effectiveness of Risk Minimisation

Besides the routine pharmacovigilance risk minimisation measures, such as the information described in the Summary of Product Characteristics (SmPC), the following additional risk minimisation measures (aRMM) are in place for Hemgenix:

A **health care professional guide**, a **patient guide** and a **patient card** are implemented in order to educate health care professionals (HCPs) and patients about the following specific risks associated with the therapy and provide guidance on monitoring these risks post-treatment.

- Hepatotoxicity
- Thromboembolic events
- Risk of malignancy in relation to vector integration in the DNA of body cells
- Germline transmission
- Transmission to third parties (horizontal transmission)
- Development of FIX inhibitors

Furthermore, the **health care professional guide** and the **patient guide** include additional guidance for the missing information of the Long-term effect.

Communication plan:

- Training of haemophilia Treatment Centres by CSL Behring Medical Affairs teams on RMP / Risk Minimisation Measures / aRMM, during the onboarding process of the centre for gene therapy
- Dissemination of HCP and patient training materials and patient cards to haemophilia Treatment centres planning to be part of gene therapy patient journey
- Dissemination of patient training materials and patient cards to haemophilia main patient organisations in EU member states, as well as European haemophilia Consortium (European umbrella patient organisation)
- Dissemination of HCP and patient training materials and patient cards via CSL Behring Hemgenix appropriate websites in EU / member states

Plans to evaluate the effectiveness of the interventions and criteria for success:

To evaluate the effectiveness of the interventions and criteria for success, CSL Behring is planning to perform a survey to evaluate the effectiveness of aRMMs for Hemgenix among prescribers in the EU[redacted]), with the objective of assessing HCP's awareness of aRMM tools, HCP's utilisation of aRMM tools, HCPs knowledge of the risk of key AEs highlighted in the Hemgenix SmPC and assessing the alignment of HCP's self-reported behaviour / practices of minimising the risks of key AEs in accordance with the SmPC.

The effectiveness evaluation study will consist of a cross-sectional survey among potential prescribers of Hemgenix. The survey will be conducted in a sample of EU countries representing the highest volume of Hemgenix use across the EU. Additional countries may be included to enhance recruitment. Data will be collected using a structured, self-administered questionnaire. HCPs will be invited to take the survey online. However, other participation modalities (eg, telephone, paper-based) may be made available to enhance participation.

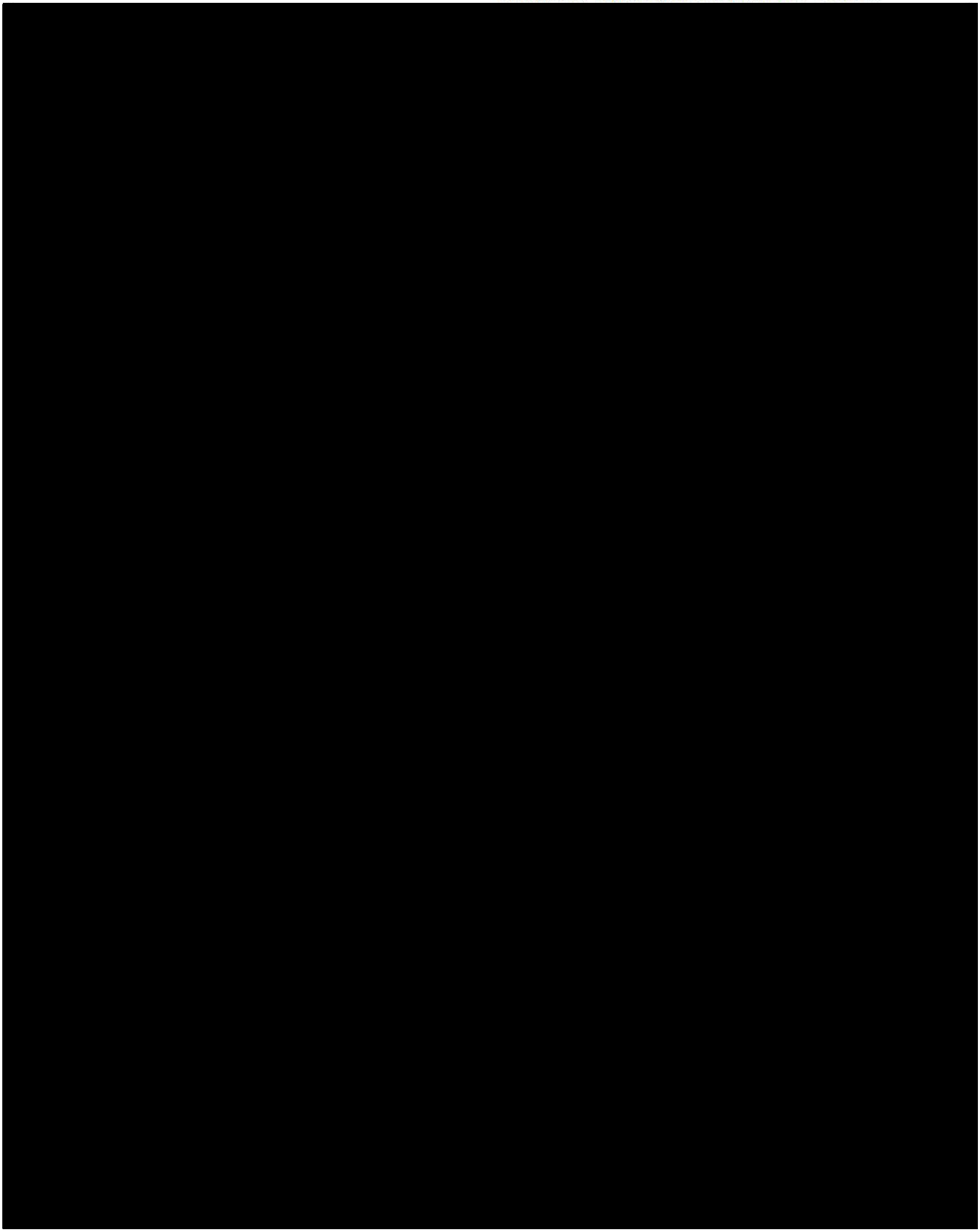
The survey will be administered 12 months after commercial launch of Hemgenix in selected EU countries to allow sufficient outreach and utilisation of the aRMM.

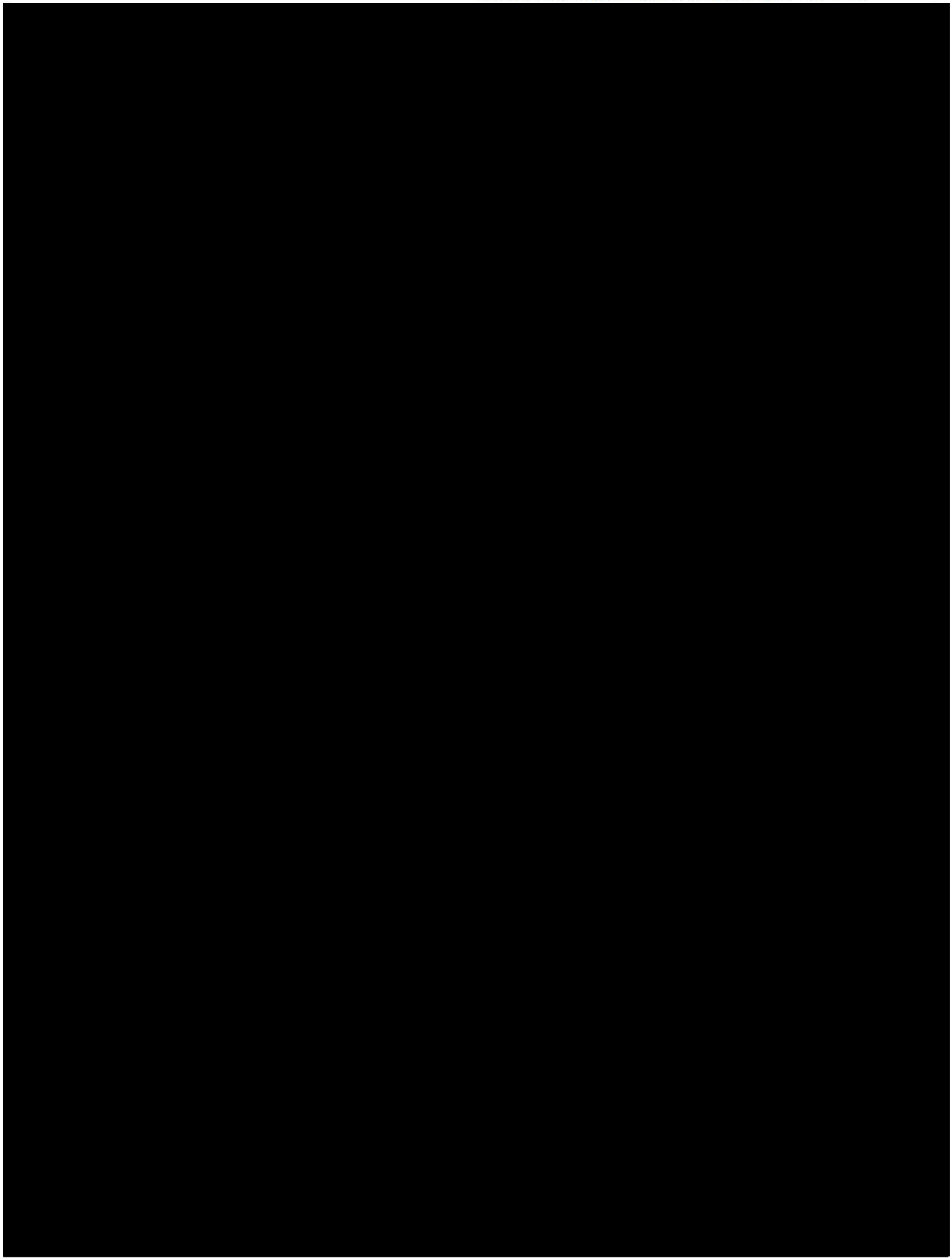
17 Benefit Evaluation

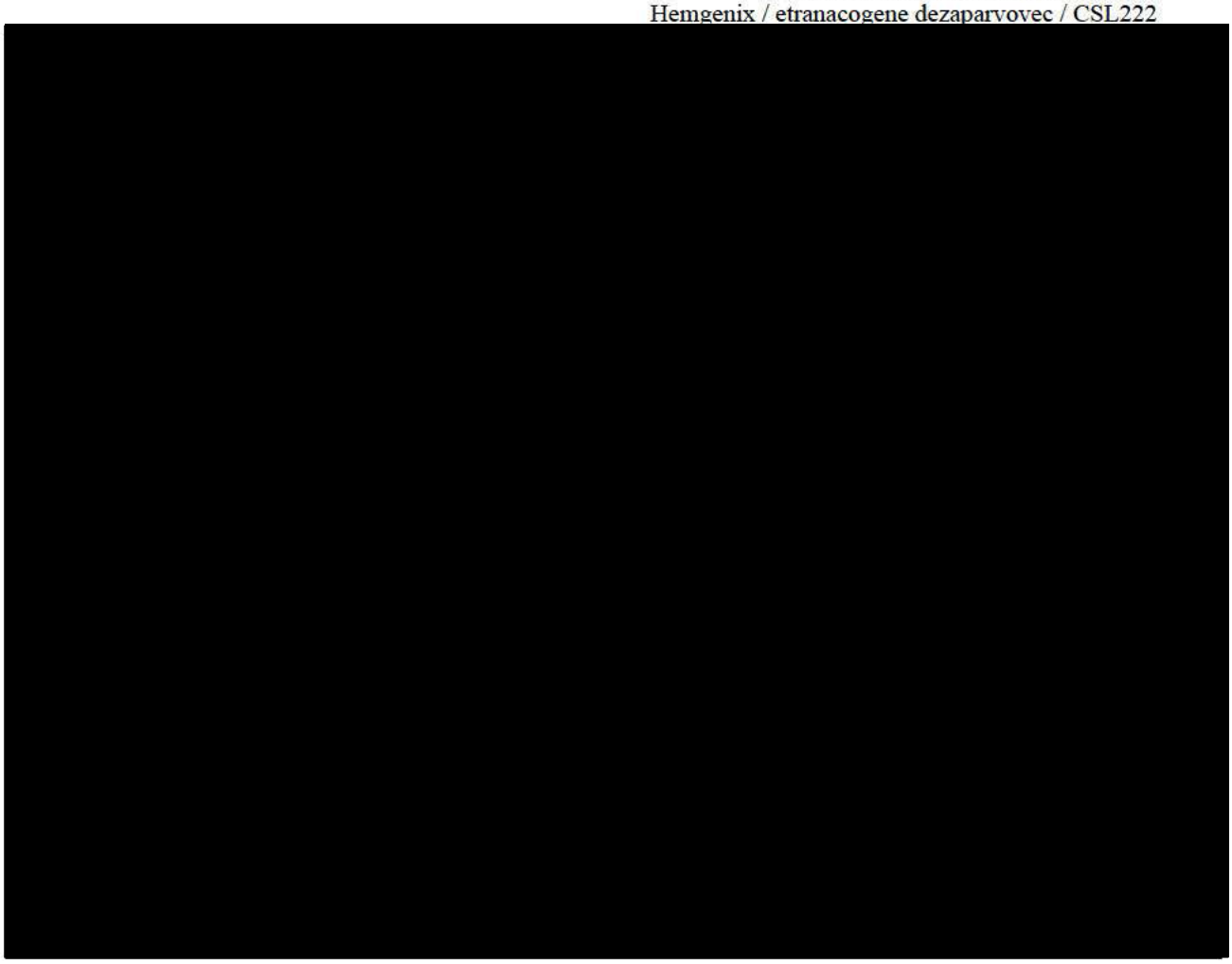
17.1 Important Baseline Efficacy and Effectiveness Information

Hemgenix is a somatic gene therapy designed to introduce the hFIX gene into hepatocytes to address the root cause of the haemophilia B disease. Hemgenix consists of a codon-optimised coding DNA sequence of the gain-of-function Padua variant of the human FIX (hFIXco-Padua), under control of the liver-specific LP1 promoter, encapsulated in a non-replicating recombinant adeno-associated viral vector of serotype 5 (AAV5). Following single intravenous infusion (IV), Hemgenix preferentially targets liver cells, where the vector DNA resides almost exclusively in episomal form. Subsequent to transduction, Hemgenix directs long-term liver-specific expression of FIX-Padua protein. As a result, it partially or completely ameliorates the deficiency of circulating FIX procoagulant activity of patients suffering from haemophilia B, restoring the haemostatic potential and limiting bleeding episodes and the need for exogenous FIX treatment.

The CSL222 clinical development program has demonstrated efficacy and effectiveness of treatment with CSL222 in subjects with severe and moderately severe haemophilia B.







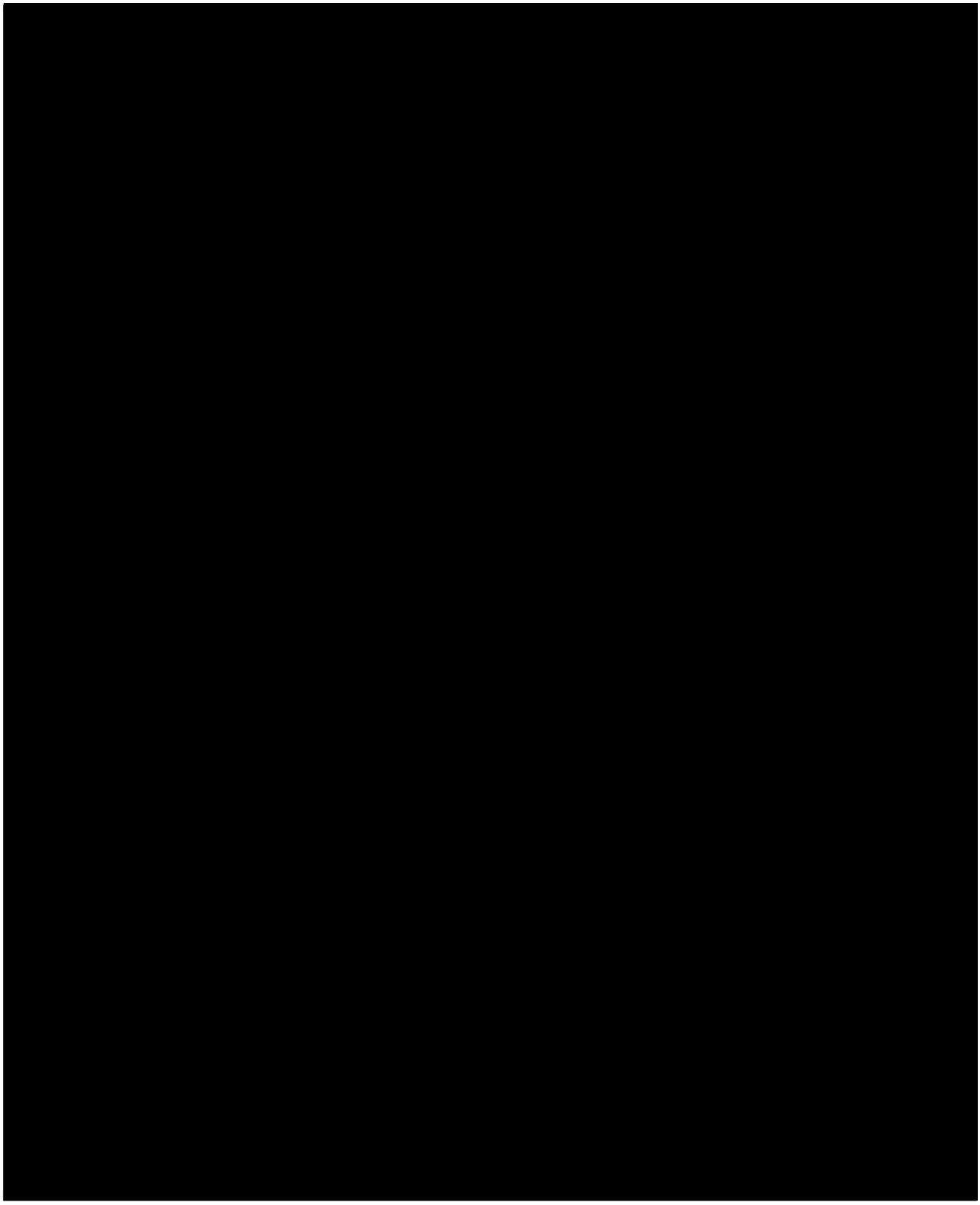
17.2 Newly Identified Information on Efficacy and Effectiveness

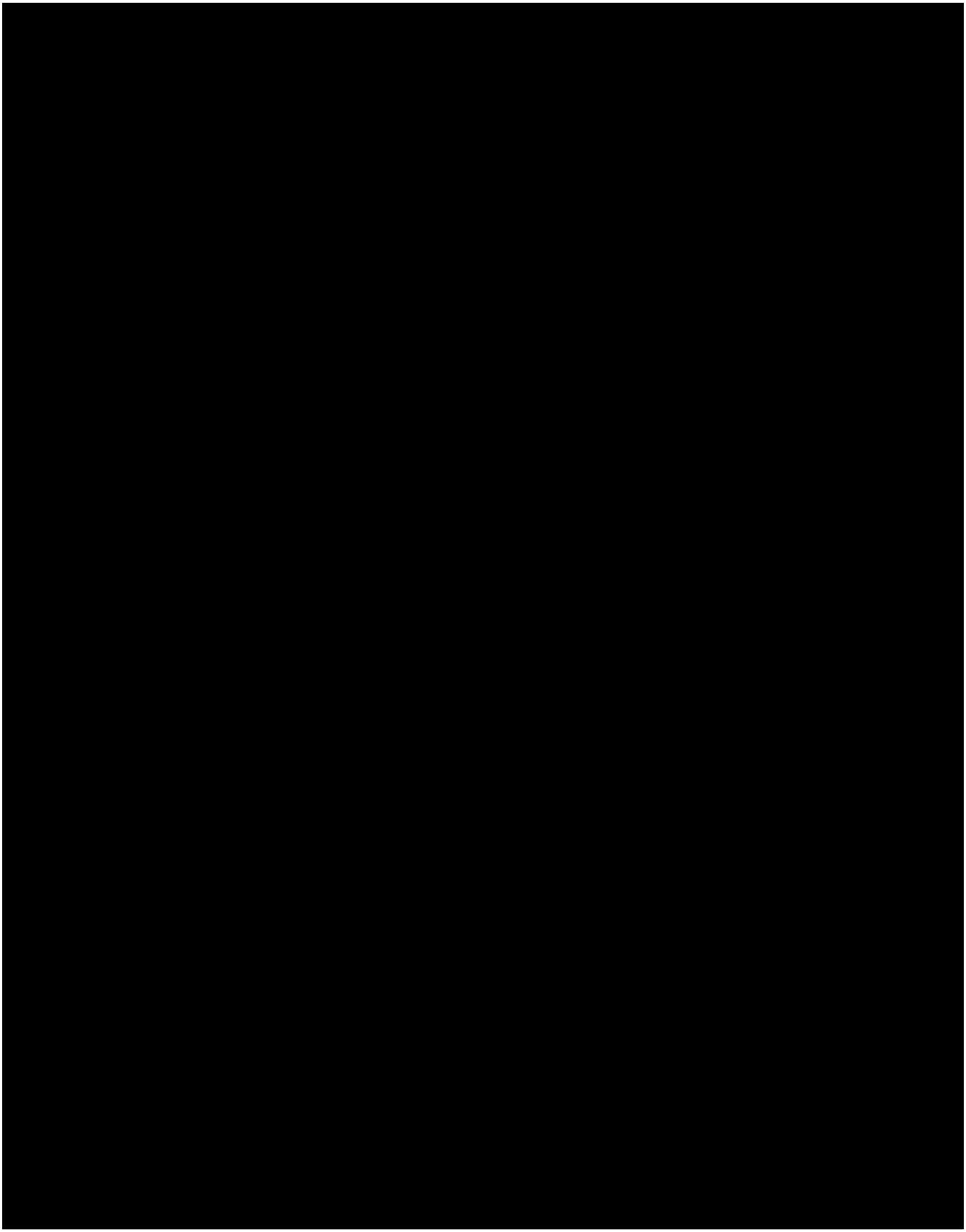
No relevant new information on the efficacy or effectiveness of Hemgenix has become available during the reporting period.

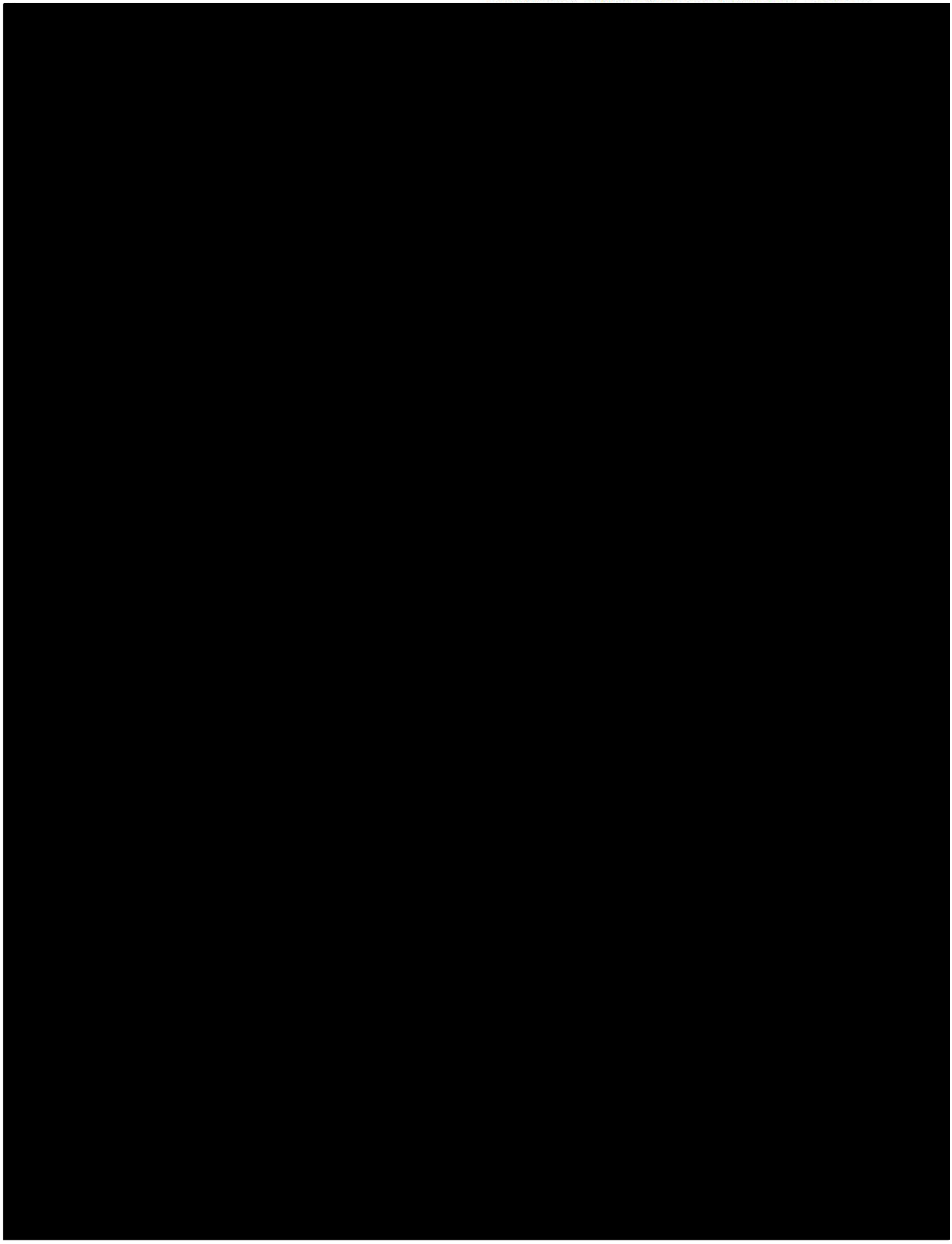
17.3 Characterisation of Benefits

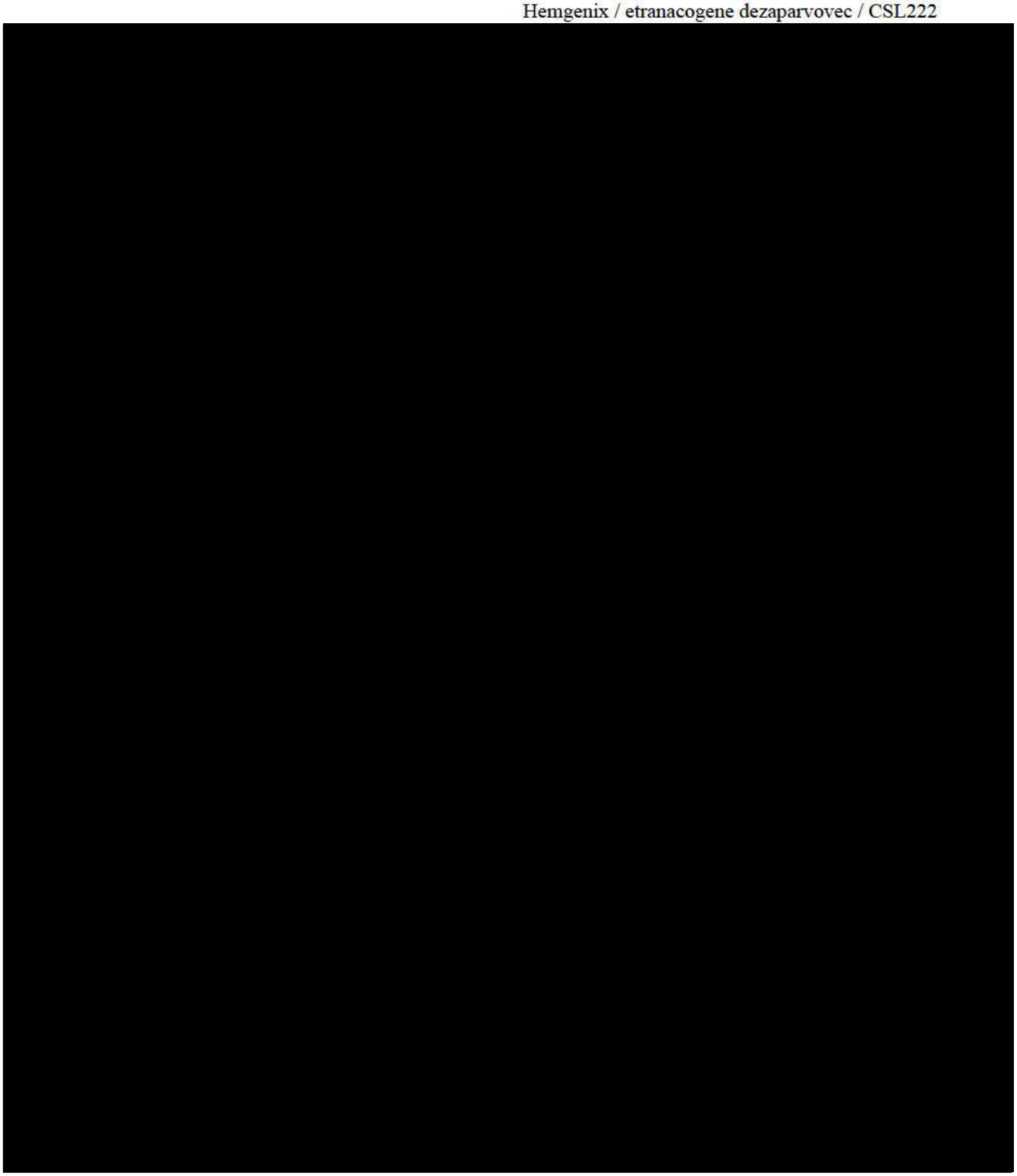
No new relevant benefit data for Hemgenix / CSL222 have become available during the reporting period. Refer to Section 17.1 for information on efficacy and effectiveness of Hemgenix / CSL222.

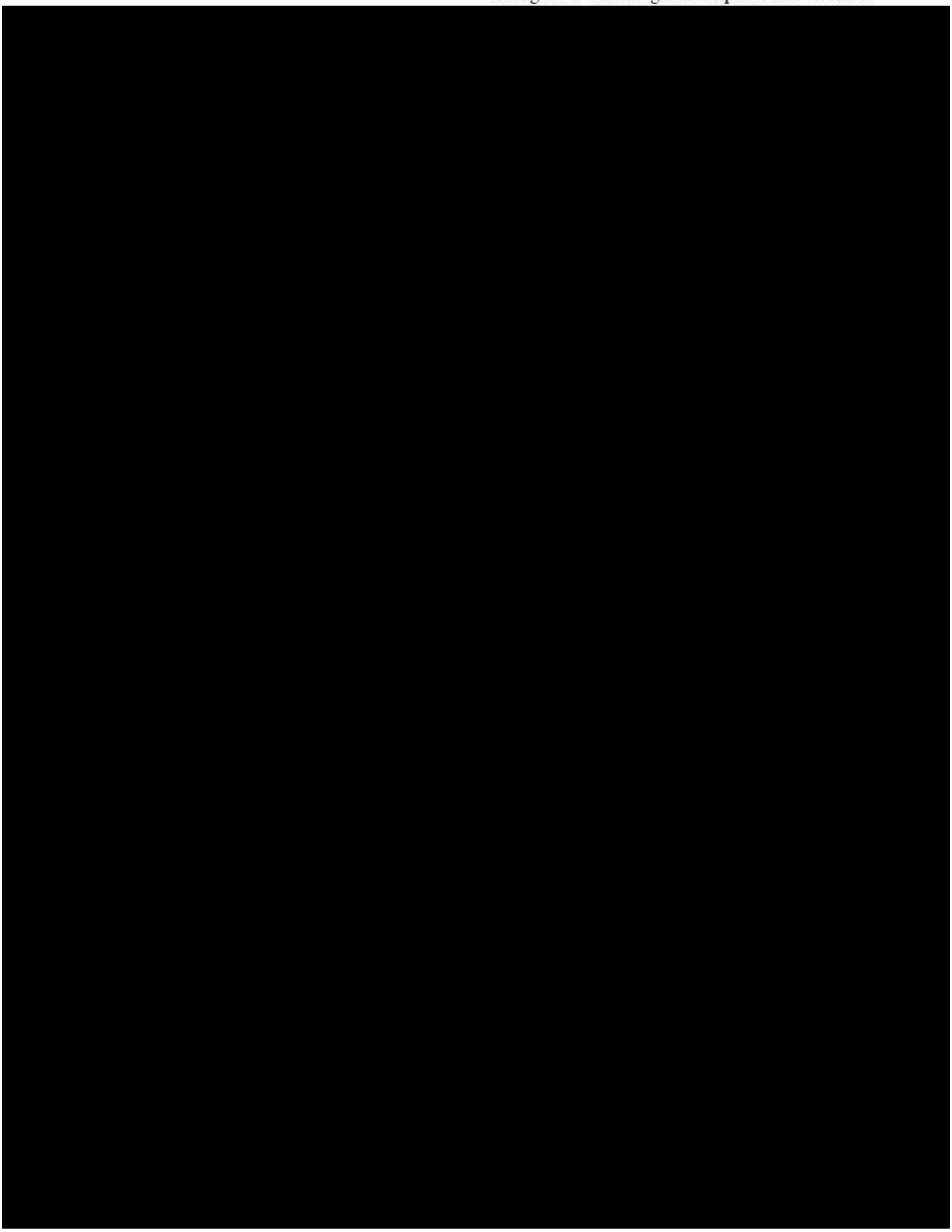
18 Integrated Benefit-Risk Analysis for Authorised Indications











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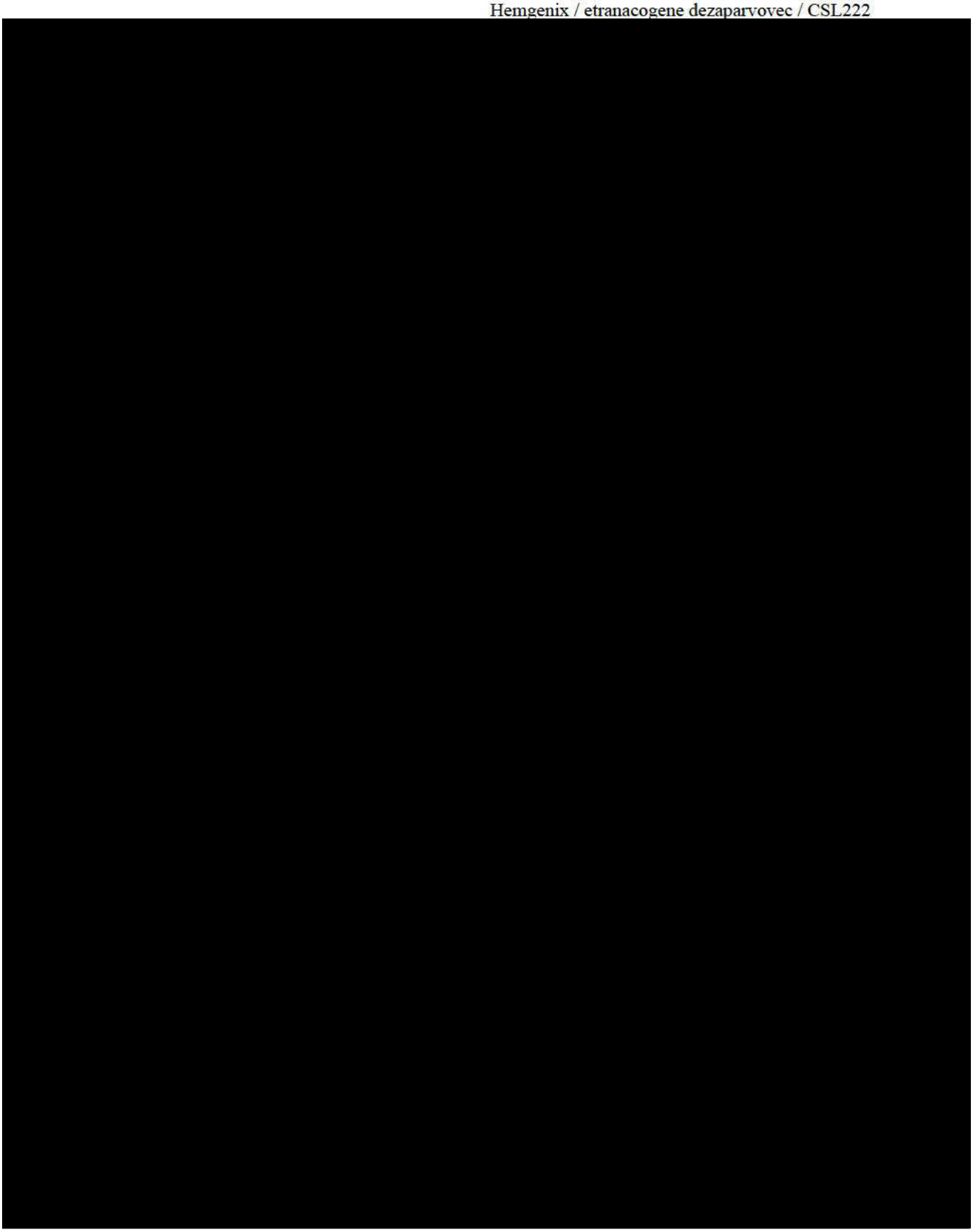

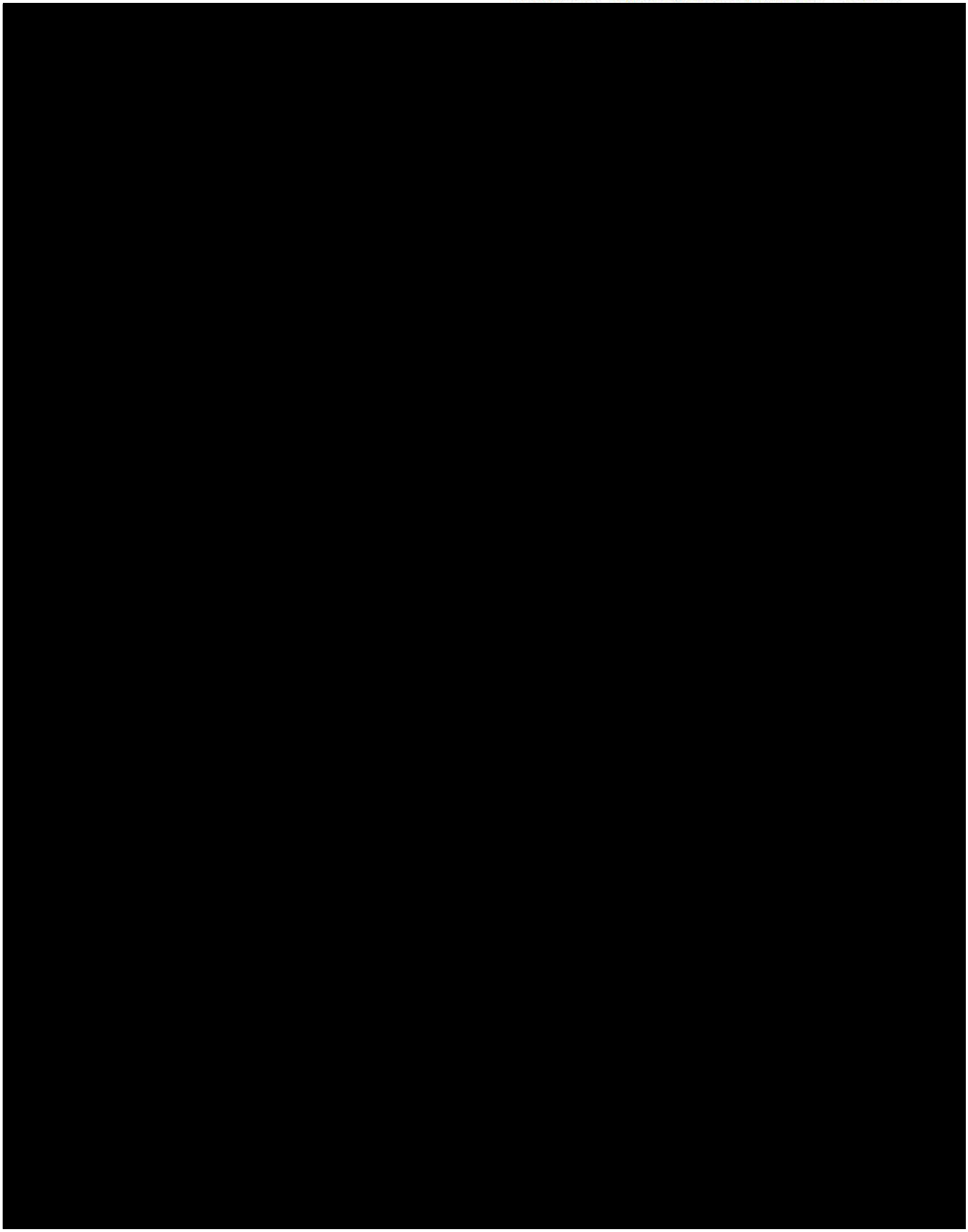

[redacted]

19 Conclusions and Actions

No new information arose during the reporting period that would change the overall evaluation of benefit-risk for Hemgenix when used in congenital FIX deficiency (see [redacted] for full indication).

Based on the evaluation of information collected during this reporting period and the cumulative data review, no changes in the benefit-risk profile for Hemgenix was observed. The overall benefit-risk analysis for Hemgenix remains favourable. No changes to the RMP are recommended. The safety profile of Hemgenix is considered adequately reflected in the current RSI and no safety amendments are warranted at present.

Signature Page

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Signed By	Date (GMT)
[redacted]	17-Jan-2025 13:05:43
Approved-EU-QPPV (or delegate) Approval	

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