

Grünenthal Response to Joint Communication from Special Procedures
Ref: AL OTH 196/2021

Grünenthal values the important mandate granted by the Human Rights Council to the Special Procedures to report and advise on human rights and to ascertain full and accurate facts with respect to specific allegations. As such, we are grateful for the opportunity to provide additional information regarding the points raised in the Special Procedures Mandate Holders' joint communication of 7 June 2021 (the "**Mandate Holders' Joint Communication**").

We act responsibly as an international healthcare company, with activities spanning the whole value chain from research and development via manufacturing to marketing and distribution in all our 29 affiliates worldwide. Everything we do stems from our sense of responsibility for our activities, meaning that we proactively strive to ensure we deliver the right medicine to the right patient. This responsible business approach also drives the way we produce and distribute our women's health portfolio in Latin America, including in the provision of medication and contraceptives. Specifically, we seek to ensure access to contraceptives for women throughout the Latin American region, especially those who otherwise would not be able to undertake family planning in a safe and reliable way. Our women's health portfolio is manufactured in line with state of the art internationally recognized regulatory and quality standards, including with respect to robust recall procedures going beyond country-specific requirements. Related to the issues raised in the Mandate Holders' Joint Communication, we empathize with and support women who experienced unwanted pregnancies, and as we describe further below, we have agreed with a Chilean NGO to provide health, educational and financial support to those women, in line with our commitment as a responsible business.

In Chile, our corporate mission has been to improve the quality of Chilean women's lives by developing and distributing women's health products in line with the highest scientific and ethical standards. By making birth control products available to the Chilean market, Grünenthal is committed to promoting women's health and to empowering women to make self-determined decisions about their reproductive health in Chile.

Grünenthal first began to operate in Chile, through its subsidiaries, in 1979. Over the intervening years, we have expanded our investment in the country, most significantly in 2013, when we acquired Laboratorios Andrómaco S.A. ("**Andrómaco**"), through which Grünenthal also holds Laboratorios Silesia S.A. ("**Silesia**"). In 2017, Grünenthal—through Andrómaco—opened a women's health products plant in Santiago, Chile, a US\$14.5 million investment dedicated to producing birth control pills and hormone replacement therapies for patients in Chile and across Latin America.

In response to the Mandate Holders' Joint Communication, below we set out information on Grünenthal's corporate governance framework, including our legal, ethical, regulatory and compliance policies, quality assurance and quality control processes, drug safety management systems and local grievance mechanisms (**Section I**). We then set out pertinent facts regarding Anulette® CD (**Section II**), Minigest® 15 and Minigest® 20 (**Section III**).

I. CODE OF CONDUCT, COMPLIANCE POLICIES, QUALITY ASSURANCE AND CONTROL, AND LOCAL GRIEVANCE MECHANISMS

Grünenthal's global business is conducted in line with its Code of Conduct,¹ compliance policies, local laws and regulations, as well as professional and industrial guidelines and directives. Our Code of Conduct—which applies to all subsidiaries—sets out clearly defined principles related to our corporate responsibility to conduct research and business activities in a legal and ethical manner. With respect to patient and drug safety, Grünenthal is committed to drug safety, quality assurance, quality control and all applicable legislative and regulatory requirements regarding product safety and labeling. Our ethical responsibilities are based on honesty in interpretation and communication, reliability in performing research, objectivity, transparency and accessibility, duty of care, data protection and confidentiality. Grünenthal also encourages employees and third parties to report the suspected violation of any pertinent standards, including anonymously via Grünenthal's Ethics Helpline.² More generally, our approach to interactions with individuals inside and outside of Grünenthal is based on a commitment to treat every person fairly and to respect and promote human rights.

In support of its Code of Conduct, Grünenthal has developed a number of company-wide compliance policies, including policies on business partners and third-party due diligence procedures, healthcare interactions, patient interactions, promotion & marketing, research and development, data protection, fair competition, anti-corruption and anti-money laundering. With respect to Grünenthal's Chilean operations, these compliance policies are supplemented by local Chilean law and regulations.

Grünenthal's business partner policy, third-party due diligence procedures and code of conduct for business partners were designed to ensure integrity and respect for the rights of individuals and to protect the environment throughout our supply chain, as well as to promote compliance with Grünenthal's commitments to, amongst other ends, drug safety and quality assurance. Our business partner policy applies to supply-side parties (*i.e.*, suppliers or vendors), sale-side parties (*i.e.*, customers or third parties that distribute, promote, commercialize, or sell Grünenthal products) and medical-side parties (*i.e.*, healthcare professionals, healthcare organizations or patient organizations that deliver services to or receive grants or donations from Grünenthal).

Through the policy, we engage in a (1) risk classification, (2) risk management and (3) monitoring process to assess and manage risk at all stages of the business relationship. All partners above a certain risk-based threshold are assessed at the outset of the relationship, when Grünenthal investigates the business partner, including by soliciting responses from the partner to a due diligence questionnaire. In light of its risk assessment, Grünenthal then determines mitigation measures in line with the level of risk posed by the business partnership. Grünenthal finally assesses whether the partner is acceptable to move forward with the relationship; if the business partner is classified above a particular risk threshold, it will be asked to review the Code

¹ Grünenthal's company-wide Code of Conduct is available here:
<https://www.grunenthal.com/en/responsibility/compliance-ethics-and-transparency>.

² More information regarding the Ethics Helpline is available here:
<https://www.grunenthal.com/en/responsibility/compliance-ethics-and-transparency>.

of Conduct for Business Partners and sign and acknowledge their agreement to comply with it.³ Specifically, that Code of Conduct for Business Partners requires that “all international and national conventions and laws in the area of fundamental rights must be adhered to.” The relationship, and the adequacy of the mitigation measures put in place to monitor the partner, is then reassessed at regular intervals, in line with the level of risk associated with the partner.

Quality in the manufacture and packaging of Grünenthal products in Chile is managed by technical controls implemented in compliance with local requirements mandated by Chile’s Institute of Public Health (*Instituto de Salud Pública*, or “**ISP**”), a public entity functioning under the Ministry of Health (*Ministerio de Salud*). Multiple controls exist at each stage of production—*i.e.*, during the product’s manufacture, during the product’s packaging, and finally before the product is authorized to be released for marketing. Quality controls during the manufacturing and packaging processes include quality checks that take place at regular frequencies, in some instances every 30 or 60 minutes. Before products can be released to the Chilean market, they are subject to a final analysis to confirm that they meet technical specifications, including the appropriate quantity of active pharmaceutical ingredients (“**API**”) as approved by ISP. Stability studies (*i.e.*, studies to confirm the continued efficacy of a product over its shelf life) are generally conducted prior to the introduction of a product to the market, as a prerequisite to receiving a marketing authorization from the Chilean authorities. The product is exposed to climatic conditions that represent permanently worst-case stress conditions in the Chilean climate and is tested at regular intervals.

As part of its commitment to patient safety, Grünenthal implements a robust local pharmacovigilance system, overseen by Grünenthal’s global Drug Safety department. Drug Safety is responsible for the set-up, maintenance, and development of the company’s pharmacovigilance system, covering the life-cycle of all medicinal products and including risk assessments and patient safety evaluations.

Finally, Grünenthal’s Chilean operations provide two means for the direct submission of complaints from purchasers and patients regarding the quality of Grünenthal products. All products are marked with the telephone number for the company’s call center, and the company’s website likewise includes a phone number as well as a submission form by which complaints may be submitted. When a complaint is received, it is triaged: if the complaint pertains to suspected quality issue, it is promptly communicated to Quality Assurance for investigation to be completed within 14 days. Quality Assurance conducts an investigation to determine whether the suspected issue is justified, and whether it is singular or may evidence a more systemic problem. The outcome of the investigation determines the company’s response.

II. THE ALLEGATIONS CONTAINED IN THE MANDATE HOLDERS’ JOINT COMMUNICATION

A. Anulette® CD

Anulette® CD (“**Anulette**”) is approved in Chile for use as an oral contraceptive and to treat menstrual disorders, dysmenorrhea, and menstrual pain. The drug functions by dispensing

³ Grünenthal’s Code of Conduct for Business Partners is available here: <https://www.grunenthal.com/en/responsibility/compliance-ethics-and-transparency>.

its active ingredients—Ethinylestradiol and Levonorgestrel—in the form of a coated tablet, taken once daily over the course of three weeks (21 days) of a four-week (28-day) cycle; during the fourth week, the patient takes a daily placebo pill. Each of the 21 active pills and seven placebo pills are packaged into a blister socket, and each blister pack therefore has 28 blister sockets and contains four weeks of contraception. The active and placebo pills are differentiated by their color: the active pills are yellow in color and the placebo pills are blue in color. As the top side of the blister pack is made with transparent foil, its content is clearly visible. When sold to institutional purchasers, as was the case for the entirety of the two batches subject to recall in 2020, ten blister packs are packaged in a single box. At the point of distribution, a healthcare worker dispenses several months’ worth of the product (or several blister packs) to a patient.

Anulette is manufactured by Andrómaco and marketed by Silesia. The ISP first granted Silesia a marketing authorization for Anulette in January 1996; this authorization has been renewed every five years since that time, with its most recent renewal occurring in January 2021. Since 2019, Silesia has distributed nearly four million blister packs in Chile to private and institutional purchasers. Institutional sales are made pursuant to contracts with the Supply Center of Chile’s National Health Services System (*La Central de Abastecimiento del Sistema Nacional de Servicios de Salud*, or “**CENABAST**”), under which Silesia distributes Anulette to Chile’s various Health Services (*Servicios de Salud*)—regional entities functioning under the Ministry of Health, which oversee public healthcare sites (*Centros Comunitarios de Salud Familiar* or “**CESFAM**”).

The production and marketing of Anulette is subject to Grünenthal’s Code of Conduct and all compliance policies as described above; as a result, the suppliers of all raw materials that are used in the manufacture and packaging of the drug are subject to risk analysis and risk management. During the course of its manufacture and production, Anulette undergoes nearly 100 controls over the course of four stages—compression, coating, blistering, and packaging—of its manufacture. Furthermore, prior to release for sale, a final analysis is conducted on each batch, pursuant to established analytical methods, to ensure that the product meets approved specifications authorized by ISP.

Prior to August 2020, Anulette batches had never been recalled in Chile. The two Anulette batches subject to recall in 2020—Batch B20034A and Batch B20035A—were respectively released for sale to institutional purchasers in March and April 2020 and were first distributed in April 2020. Silesia and Andrómaco learned of an issue with the packaging on 24 August 2020, when they received a mandatory recall notice for Batch B20034A on the basis of a 6 August 2020 complaint logged with ISP by CESFAM Piedra del Aguila, identifying alleged defects in six blister packs, including instances of empty blister sockets, crushed pills, and blisters in which one placebo and active-ingredient pill were positioned in incorrect blister sockets within the blister pack.

The Batch B20034A recall was designated as a “Class 2” recall, defined by the ISP as a situation in which use of the recalled product may cause temporary adverse health consequences, or where the probability of the recalled product causing serious adverse health consequences is remote.⁴ In line with this designation, a recall took place at the distributor (rather than, for

⁴ ISP Resolution 5173, available at <http://bcn.cl/2f1tw>.

example, the patient) level. In particular, ISP's recall notice and related communications required Silesia and Andrómaco to recall and destroy all recovered product, submit specified documentation regarding the recalled batch to ISP and conclude within 30 days an investigation into the causes of the defects reported by CESFAM Piedra del Aguila. Notice of the recall was also published on Silesia's website.

On 31 August 2020, contacts at a second CESFAM, CESFAM Apoquindo, informally notified an Andrómaco employee of similar defects in product from a second batch, Batch B20035A. Silesia accordingly initiated a voluntary recall of Batch B20035A. After this decision was communicated to ISP, ISP issued a notice of the voluntary recall, which was also publicized on Silesia's website. Again, the recall was Class 2, which obligations therefore mirrored those of the initial mandatory recall. Silesia provided required documentation to ISP, notified distributor clients who had received Batch B20035A of the recall, organized the return of undistributed product and included Batch B20035A in its investigation into the root cause of the reported defects.

As a result of the investigation, the packaging of 12 individual blister packs across both recalled batches were found to be defective. To prevent a recurrence of these packaging issues, in early September 2020 Andrómaco installed two devices on the blistering machines used to package Anulette to prevent pill displacement: (1) vibration sensors that automatically stop the machine in the event of vibration of blisters that contain active and placebo pills but have yet to be sealed with the underlying aluminum foil; and (2) a locking plate to prevent tablets from leaving the blister cavity. Andrómaco has since undertaken a complete revalidation of the manufacturing process, which was received, reviewed and accepted by ISP prior to lifting the suspension of Anulette's marketing authorization in November 2020. To afford additional protection, Andrómaco will install a second verification camera in the fourth quarter of this year to observe the blistering process.

Notably, given the transparent covering of the blisters, defect in the recalled batches is entirely observable by visual inspection by both healthcare workers and patients: a crushed or missing pill or an irregular number of active (yellow) pills and placebo (blue) pills is apparent on each blister's face, and each blister pack must be removed from the packaging in order to be distributed by healthcare workers to patients. In early September 2020, ISP therefore re-authorized the distribution of the non-recalled batches of Anulette, provided that individual healthcare workers undertook a visual quality control check before distributing the blister packs to patients. Of the blister packs returned from purchasers following the recall of batches B20034A and B20035A, a representative sample of approximately 20,000 blister packs was visually inspected and no defects were identified. A total of 52 individuals submitted complaints to ISP and Chile's national consumer protection agency (*Servicio Nacional del Consumidor* or "SERNAC") related to suspected Anulette quality defects. Of these complaints, two were reported by healthcare workers related to broken active pills, while 28 were determined not to be significant (relating, for instance, to pill discoloration or loss of film coating). All 52 individuals submitted their complaints after the recall notice.

We recently reached a binding agreement with a Chilean NGO, whereby certain women who became pregnant in 2020 will receive health and educational support, including monetary compensation. More than 85% of the women named in the Mandate Holders' Joint Communication will receive support pursuant to this agreement.

B. Minigest® 15 and Minigest® 20

Minigest® 15 and Minigest® 20 (“**Minigest 15**” and “**Minigest 20**,” together, the “**Minigest Contraceptives**”), which Andrómaco no longer produces, were both approved in Chile for use as oral contraceptives. The Minigest Contraceptives’ APIs were Ethinylestradiol and Gestodene, estrogen and progestin widely used in birth control pills; Minigest 20 contained the higher dosage of API.⁵ Ethinylestradiol was sourced from Aspen Oss BV Diosite in Holland and Gestodene was sourced from Zhejiang Xianju Pharmaceutical in China. The ISP first issued marketing authorizations for Minigest 15 in 2003 and for Minigest 20 in 2007; these authorizations were in place and renewed every five years until Andrómaco voluntarily suspended distribution of the products (as we describe below).

Between 2014 and 2020, Andrómaco sold over 162,500 blister packs of the Minigest Contraceptives in Chile. Of these sales, 4,787 blister packs were sold from the batches subject to voluntary recall in October 2020: 2,623 blisters of Minigest 15 and 2,164 blister packs of Minigest 20.

In August 2020, Andrómaco concluded its stability studies for the Recalled Minigest Batches, which determined that the API of the contraceptives fell below the approved specification in the climatic chamber after a certain period of months under permanent climatic conditions that represent worst-case stress conditions in the Chilean climate. Andrómaco initiated an investigation to determine the measures it should adopt in response to the stability results. In addition, Grünenthal conducted a drug safety risk assessment as part of this internal process in which it also considered the potential impact unintended pregnancies could have on individual patients and Chilean society as a whole, especially given the medical, emotional, social and financial costs on women, family and society from a human rights perspective.

Accordingly, Andrómaco initiated a Class 2 voluntary recall of the Minigest Contraceptives. Andrómaco informed the ISP of this decision in late September 2020, and on 5 October 2020, the ISP issued the voluntary recall notice. In a related publication, ISP stated (as translated):

“manufacturers have the obligation to undertake stability studies in real time for commercialized pharmaceutical products, in order to verify that their quality attributes are sustained throughout their established efficacy periods. It should be noted that the series affected by the voluntary recalls were released for distribution in compliance with all parameters mandated by the health registry, and that this decrease in the potency of the active ingredients came about in the course of the stability studies for both products.”

In January 2021, the ISP initiated administrative proceedings against Andrómaco in respect of the Recalled Minigest Batches. These proceedings remain ongoing. In March 2021, Andrómaco officially discontinued its production of the Minigest Contraceptives. The decision

⁵ Minigest 20 contained 0.020mg of Ethinylestradiol and 0.075mg of Gestodene. Minigest 15 contained 0.015mg of Ethinylestradiol and 0.060mg of Gestodene.

to do so pre-dated the voluntary recall and was based on commercial considerations as part of a wider consolidation of Grünenthal's portfolio in Chile. To date, one complaint was submitted by a member of the public in respect of the Recalled Minigest Batches. This complaint related to side-effects experienced by the patient after taking Minigest 20 and was submitted in November 2020 to SERNAC following the ISP's recall alert. No complaints were registered before the recall. More generally, only one other complaint was submitted in respect of the Minigest Contraceptives since 2014: in June 2019, a customer complained of a faulty blister packaging as the aluminum film had peeled off.

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Grünenthal and its Chilean subsidiaries are committed to developing and distributing women's health products according to the highest scientific and ethical best practice. We are constantly developing and improving our systems in order to continue to provide safe and effective contraceptive products to women in Chile to support women's rights to make autonomous decisions about their health and their families.

We appreciate having received the opportunity to provide further information on these important matters.