Presidency of the Council of Ministers

RESPONSE TO MINISTRY OF HEALTH QUESTION ON THE USE OF TRYPTORELIN IN THE CASE OF A DIAGNOSIS OF "GENDER DYSPHORIA"

November 22, 2024

Presentation

This paper responds to a question formulated by the Ministry of Health on Dec. 22, 2023 regarding the ethicality of the use of the drug tryptorelin in cases of gender dysphoria for minors (see Annex 1).

A working group was formed, coordinated by Professors Assunta Morresi and Luca Savarino.

A number of experts with different professional backgrounds inherent to the topic were heard: Prof. Andrea Lenzi - Professor Emeritus of Endocrinology at the University of Rome "La Sapienza", Chairman of the National Committee for Biosafety, Biotechnology and Life Sciences; Prof.ssa Antonella Costantino - Child Neuropsychiatrist, Director of the Complex Structure of Neuropsychiatry of Childhood and Adolescence at the Policlinico di Milano; former President of the Italian Society of Neuropsychiatry of Childhood and Adolescence (SINPIA); Prof. Francesco Frasca - Full Professor of Endocrinology at the University of Catania, Head of the Complex Operative Unit of Endocrinology at ARNAS (Azienda di rilievo nazionale ad alta specializzazione) Garibaldi Nesima, in Catania, founder at the same hospital of the multidisciplinary team for gender dysphoria; Prof. Roberto Baiocco - Full Professor of Developmental and Educational Psychology at the Faculty of Medicine and Psychology of Sapienza University. Psychologist, member of the Board of Directors of the Italian Society for Gender, Identity and Health (Sigis); Prof. Fabio Monticelli **-** Psychiatrist psychotherapist, teacher in the schools of specialization in psychotherapy in Rome, Turin, Milan and Como. President of the Italian Society of Cognitive Behavioral Therapy, Adjunct Professor of Psychiatry at the European University of Rome; Dr. Carla Bizzarri - Pediatrician endocrinologist at the Bambin Gesù Children's Hospital in Rome, Head of the Simple Operative Unit of Pediatric Endocrinology; Prof. Nicolino Rossi - Former full professor of Clinical Psychology at the Faculty of Medicine of the University of Bologna. Currently professor at the Alma Mater of Bologna and Vice President of the Italian Psychoanalytic Society (SPI).

The topic was discussed during 2024 Plenaries on February 22, April 19, May 23, July 11 and 12, September 26 and 27, October 24, and November 20 and 21.

The opinion was approved by a large majority of those present, Profs. Vescovi, Navarini, Di Segni, Barone, Battaglia, Calabrò, Cantelmi, Casale, Da Re, De Marinis, De Renzis, Garattini, Garavaglia, Leonardi, Manazza, Menorello, Morresi, Petrini, Ricciuti, Ruggieri, Savarino, Scaraffia, and Semplici. A dissenting opinion was expressed by Prof. Mori.

Among those absent at the time of the vote - Professors: Ronco, Canestrari, d'Avack, Nanni Costa, Gambino, Razzano, Di Pietro, Zuffa, Caporale - subsequently, Professors: Ronco, Canestrari, d'Avack, Nanni Costa, Razzano, Caporale expressed a favorable opinion; Professors Di Pietro, Zuffa declared an abstention.

Although not entitled to vote, the following joined: for the President of the ISS, the delegate, Dr. Mauro Biffoni; for the President of the FNOMCeO, the delegate, Dr. Guido Giustetto; absent from the plenary, they joined later for the President of the FNOVI, the delegate Prof. Bernasconi and for the President of the CNR, the delegate Prof. Maga.

The paper is accompanied by a dissenting note from Prof. Mori, an abstention note from Prof. Zuffa, and two explanations of vote. The first explanation of vote is signed by 15 components: Calabrò, Cantelmi, Casale, De Marinis, De Renzis, Leonardi, Manazza, Menorello, Morresi, Navarini, Petrini, Razzano, Ricciuti, Ronco, Ruggeri. The second is signed by 7 members Barone, Battaglia, Canestrari, Caporale, d'Avack, Garattini, Savarino, with the membership of the 4 non-voting members: Bernasconi, Biffoni, Giustetto, Maga.

Prof. Angelo Luigi Vescovi President
of the CNB

With this paper, the CNB responds to a question formulated by the Ministry of Health regarding the advisability of "reexamining the question of the ethicality of the use of the drug tryptorelin in cases of gender dysphoria for minors, particularly considering the sensitivity of the issue, which concerns minors who are going through a decisive stage of their development, and concerns their awareness in giving their consent to this pathway."

It should be noted that different orientations are present in the CNB, reflecting the important international debate still underway on issues related to gender identity, especially in minors: it is not possible, however, to bring out the aforementioned orientations in the context of an answer to a pointed question. In fact, the Ministry's request clearly refers to a perimeter circumscribed to the permissibility of the use of tryptorelin; in its response, the CNB has therefore limited itself to evaluations concerning the use of this specific drug, deciding not to engage in a philosophical and bioethical reflection on gender as well as on transitional choices and pathways here.

As also mentioned in the question, on July 13, 2018, the CNB published a document titled "*Regarding Aifa's request on the ethicality of the use of the drug triptorelin for the treatment of adolescents with gender dysphoria*." In it, the CNB addressed the issue of the *off-label* use of tryptorelin within the so-called "Dutch protocol," which provides puberty blockade for minors diagnosed with gender dysphoria[1]. Henceforth, in this paper, when talking about prescription/administration of tryptorelin and puberty blockade, reference will be made to the *off-label* use of the drug, paid for by the National Health Service, as defined by AIFA Determination 21756 of 2019, which incorporated the indications of the 2018 CNB opinion.

In it, against the potential benefits of using tryptorelin for the treatment of gender dysphoria in adolescents, elements of uncertainty had been identified, including the paucity of safety and efficacy studies and insufficient *follow-up* data of treated cases. In subsequent years, the relationship between the benefits and risks of tryptorelin continued to be debated, giving rise to a major international confrontation in the scientific community, which had different outcomes: the use of tryptorelin was discontinued or limited in the United Kingdom, Sweden, Finland, and Norway, while other countries did not see fit to drastically reduce its use, e.g., Canada, the Netherlands, Belgium, Switzerland. In general, all these countries used or still use this drug consistently with the "Dutch protocol," but often, in practice, in ways that are heterogeneous among themselves and with respect to Italy, also in view of the different organization and articulation of National Health Systems.

The CNB deemed it appropriate to review the specific issue referred to in the question, also in light of numerous expert hearings[2] who represented a plurality of

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[1] For i details of the protocol, v. opinion CNB of 2018 https://bioetica.governo.it/media/3739/p132_2018_triptorelina-per-adolescenti-con-disforia-di-genere_it.pdf

[2] April 19, 2024:

Prof. Andrea Lenzi - Professor Emeritus of Endocrinology at the University of Rome "La Sapienza", Chairman of the National Committee for Biosafety, Biotechnology and Life Sciences. May 23, 2024*:*

Prof. Antonella Costantino - Child neuropsychiatrist, director of the complex structure of neuropsychiatry of childhood and adolescence at the Policlinico di Milano; former president of the Italian Society of Neuropsychiatry of Childhood and Adolescence (SINPIA);

Prof. Francesco Frasca - Full professor of endocrinology at the University of Catania, Head of the Complex Operative Unit of Endocrinology at ARNAS (Azienda di rilievo nazionale ad alta specializzazione) Garibaldi Nesima, in Catania, founder at the same company of the multidisciplinary team for gender dysphoria.

July 11, 2024:

approaches to the issue of gender dysphoria in minors, referring especially to the use of tryptorelin.

In outlining the state of the art, all of the hearings, although there were marked differences in their contributions, due first and foremost to the wide range of professional backgrounds expressed, and while not disregarding other scientific contributions and other reviews, referred to a recent report known as "The Cass Review"[3]. "*The Cass Review - Independent* review *of* gender identity *services for children and* young people" is an independent review of services dealing with gender identity in children and young people within the British National Health Service. The "Review" includes a systematic review of the relevant scientific literature and addresses the issue of gender identity in children and the services that support them in the UK, including puberty-blocking protocols involving the use of drugs such as tryptorelin. The "Review" is not the only significant contribution within the literature on the use of tryptorelin, but it is certainly among the most relevant at this time, not least because of the heated discussion it has provoked within the scientific community.

Also on the basis of the hearings held, the CNB highlights the insufficiency of scientific data on the use of puberty blockers and the need to strengthen them, reiterating the need, highlighted in the scientific literature from multiple fields, for further trials. In particular, it was emphasized that it is important to clearly identify all outcomes (outcomes) of the trials, focusing on both psychological and cognitive aspects as well as those related to physical development, and the relationships between the former and the latter. In this perspective, the CNB notes that the data provided by the regions on the use of tryptorelin on minors with gender dysphoria in Italy, in the period from 2019 to 2023, are very deficient and fragmentary.

Leaving aside here the different positions on the general bioethical evaluation of the introduction of tryptorelin for gender dysphoria, the Committee, which already suggested in its 2018 opinion the promotion of safety, efficacy and *follow-up* studies, stresses the need for the Ministry of Health to take charge of funding independent studies aimed at obtaining diriment data on the efficacy and risks of the drug's administration.

Since it is not up to the CNB to define precisely the design of the experimental studies to be carried out, we limit ourselves here to some general remarks of ethical significance.

First of all, it is necessary to fund studies of higher quality than those that have already been carried out, which do not appear adequate to the objective.

Prof. Roberto Baiocco - Full Professor of Developmental and Educational Psychology at the Faculty of Medicine and Psychology of Sapienza University. Psychologist, Member of the Board of Directors of the Italian Society for Gender, Identity and Health (Sigis);

Prof. Fabio Monticelli - Psychiatrist psychotherapist, lecturer in the schools of specialization in psychotherapy in Rome, Turin, Milan and Como. President of the Italian Society of Cognitive Behavioral Therapy, Adjunct Professor of Psychiatry at the European University of Rome.

July 12, 2024:

Dr. Carla Bizzarri - Pediatric endocrinologist at the Bambin Gesù Children's Hospital in Rome, Head of the Pediatric Endocrinology Simple Operating Unit;

Prof. Nicolino Rossi - Former full professor of Clinical Psychology at the Faculty of Medicine, University of Bologna. Currently professor at the Alma Mater of Bologna and vice president of the Italian Psychoanalytic Society (SPI).

[3] Cass Review, at https://cass.independent-review.uk/home/publications/final-report/; Taylor Review (2024) at https://adc.bmj.com/content/109/Suppl_2/s73; in general, for the work of the Independent Commission https://cass.independent-review.uk/

It should also be recalled that, from a methodological point of view, the reference model for drug licensing clinical trials (the so-called *gold standard*) is a double-blind randomized controlled clinical trial. Regarding the issue of "blinding," with respect to which, with reference to this experimental setting, different assessments have emerged within the CNB, several solutions may be formulated, the choice of which will be left to the decision makers of the experimental strategy and the opinion of the ethics committees and the competent authority.

In order to better design and optimize the randomized trial, in addition to the routine systematic review of studies, the CNB considers it appropriate to also proceed with the systematic analysis of all data on past and current treatments in the Italian context, in the most complete and accurate form possible, as well as to use currently available prospective observational studies.

Within the trial, as well as in any clinical practice outside of it, special attention must be paid to the psychotherapeutic/psychological, and possibly psychiatric, pathway that might lead to the use of tryptorelin: the decision-making process must always be thoroughly documented in all its steps.

A suitable sample size should also be ensured, including the use of multicenter studies; and it is essential to differentiate each trial by sex[4].

In conclusion, given the uncertainty about the risk/benefit ratio of tryptorelin puberty blockade, the CNB would like to see prescriptions only within the framework of trials promoted by the Ministry of Health and for patients to adhere to them[5]. The CNB also recommends that the prescribing of puberty blocker, regardless of the experimental strategy chosen or the nature of the study, should be done prudently, ensuring that patients are always evaluated and followed by a multidisciplinary team, and that they receive appropriate psychological, psychotherapeutic, and possibly psychiatric intervention, which is essential prior to the decision to prescribe the drug in order to assess its appropriateness. Such interventions are equally necessary during the medication phase and even after it, in the best interest of the health of the adolescent, who is undoubtedly in a difficult phase of his or her life. The CNB also recommends that the prescription of tryptorelin should take place only after psychological therapies/psychosocial and possibly psychiatric interventions have not proven effective. The methodology just described-i.e., the use of multidisciplinary clinical evaluations and the prescription of tryptorelin only after psychological and/or psychiatric therapies have been found to be ineffective-should also be ensured in the event of administrations outside of trials, i.e., in the case of denial of consent to the trial or following specific clinical evaluations by the physician,
That should always be represented in the data collection.

In the latter cases, the CNB recommends that all data related to access to treatment, the entire course and the following *follow-up* should always be transmitted to a dedicated registry established at the Ministry of Health or at one of the relevant public health institutions, such as ISS, AIFA, Agenas, etc.

[4] The literature shows that issues concerning gender identity in minors overwhelmingly affect girls.
[5] Juvenile subjects must be recruited in compliance with current legislative provisions regarding informed consent.

Ministero della Salute

Cabinet Office

To the National Bioethics Committee

SUBJECT: Requested opinion on the use of tryptorelin in the case of the diagnosis of "gender dysphoria"

On April 10, 2018, the Italian Medicines Agency (AIFA) requested an opinion from the National Bioethics Committee (CNB) regarding the ethicality on the use of the drug tryptorelin (gonadotropin-releasing hormone analog) for the treatment of adolescents with gender dysphoria.

The CNB responded to the question with its opinion of July 13, 2018 "On the request of AIFA on the ethicality of the use of the drug triptorelin for the tranament of adolescents with gender dysphoria," approved with only one dissenting vote, on the basis of which AIFA Determination No. 21756/2019, published in the Official Gazette of the Italian Republic No. 52 of March 2, 2019, "Inclusion of the drug triptorelin in the list of medicines that can be fully paid for by the National Health Service, pursuant to Law No. 648 of December 23, 1996, for use in selected cases in which puberty is incongruent with gender identity (gender dysphoria), with a diagnosis confirmed by a multidisciplinary and specialized team and in which psychological, psychotherapeutic and psychiatric care is not resolving."

In subsequent years, some European countries, which had already been adopting this drug for some time in cases of gender dysphoria in minors, having found important critical issues have revised their protocols, in whole or in part: these include Sweden, Finland, and Norway, while in the United Kingdom an Institutional Study Commission is still at work examining the different aspects of the treatment, with an initial interim report already published, which highlights many controversial issues.

Given the emergence of this international debate, the Ministry of Health deemed it appropriate to hear in December the presidents of a number of scientific societies involved, in various capacities, in the issue of gender dysphoria in adolescents - Italian Society of Obstetrics and Gynecology (SIGO); Italian Psychoanalytic Society (SPI); Italian Society of Pediatrics (SIP); Italian Society of Gender, Identity and Health (SIGIS); Italian Society of Pediatric Endocrinology and Diabetology (SIEDP); Italian Society of Andrology and Medicine of Sexuality (SIAMS); Italian Society of Neuropsychiatry

of Childhood and Adolescence (SINPIA); Italian Society of Behavioral and Cognitive Tempia **(SITCC).**

During the hearings, different positions emerged among the respondent societies, some in favor and some not in favor of the use of tryptorelin in cases of gender dysphoria among adolescents, with different arguments and owith a general emphasis on the scarcity, at present, of scientific studies on the long-term effects of such treatment.

In Iuce of the framework outlined above, the CNB is asked whether it deems it appropriate to reexamine the issue of the ethicality of the use of the drug triptorelin in cases of gender dysphoria for minors, particularly considering the sensitivity of the issue, which concerns minors who are going through a decisive stage of their development, and concerns their awareness in giving **their consent to** this pathway.

We reserve the right to send the data, requested from the Regions and Autonomous Provinces of Trento and Bolzano, on clinical and expenditure monitoring in the period January 1, 2019 - December 31, 2023, related to triptorelin prescriptions, in off-label regimen, in the indication "for use in selected oases in which puberty is incongruent with gender identity (gender dysphoria), according to Determination No. 21756/2019, published in the Official Gazette of the Italian Republic No. 52 of March 2, 2019."

In thanking you, this opportunity is taken to extend cordial greetings.

CAP. "OB GA. BINETTO
Dott. Marco Mattei

Explanation of vote

We find it necessary to contextualize and integrate the response to the Ministry of Health's question on the use of triptorelin, both to clarify the reasons that led us to formulate and approve its contents, and to address the issue of minors' "awareness" "in giving their consent to this pathway," a topic that the CNB addressed only indirectly, having decided not to deal with transitional choices.

The issue of informed consent of the child in the context of gender transitions would require dedicated reflection[6]: here we can only limit ourselves to pointing out in broad strokes some of the main findings.

First, some general remarks.

We believe that the decision to begin a gender transition early[7] risks predisposing a child to persist in the transition process.[8]. We also think that a minor, especially one in a state of distress and with significant comorbidities such as those often associated with gender dysphoria, is unlikely to have a full awareness of the consequences of gender transition for his or her future life: many of the physical changes planned and undertaken are irreversible, and impaired fertility is often unavoidable.

Consequently, under these conditions, informed consent risks being reduced to a merely formal act, making it ethically unacceptable to allow minors to undertake gender transitions.

Second, in the specific case posed in the Ministry of Health question, the lack of firm data on the risk/benefit ratio of tryptorelin for gender dysphoria makes the situation even more problematic with respect to one of the cardinal principles of bioethics: *Primum non nŏcēre*.

Specifically: tryptorelin was introduced with the motivation of prolonging the diagnosis phase of dysphoria, assuming its reversibility, similar to its use for several other clinical indications, but at the moment even on this aspect there are scientific uncertainties. On the other hand, almost all of those given tryptorelin continue with cross-sex (masculinizing or feminizing) hormones, that is, with a partly irreversible transition path. Its use, therefore, becomes functional in anticipating gender transition at the threshold of puberty, rather than merely delaying sexual development.

In this context, we believe that free and informed choice on the part of the child is even less feasible.

Insufficient data, however, has unfortunately not prevented the use of blockers within the Dutch protocol so far; on the contrary, their use has spread to many countries.

Therefore, it is decisive to proceed with a trial of this drug, conducted in the terms indicated by the CNB Response: only in the face of a rigorous trial of tryptorelin that proves the prevalence of risks over benefits, and/or its lack of efficacy, with respect to gender dysphoria in minors, will the

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[6] The literature on informed consent (or informed assent) of minors is endless. In general, from an ethical and legal point of view, we limit ourselves to mentioning the Oviedo Convention, Art.6(3), and L. 217/2019, Art.3. Regarding the informed consent of minors in gender transitions, we point out in particular: S. B. LEVINE, E. ABBRUZZESE & J. W. MASON (2022*) Reconsidering Informed Consent for Trans-Identified Children, Adolescents, and Young Adults, Journal of Sex & Marital Therapy*, 48:7, 706-727, DOI: 10.1080/0092623X.2022.2046221.

[7] A gender transition process generally involves social transition, then puberty blockage, cross-sex hormones, and surgery.

[8] See, e.g., S. B. LEVINE et al. in note 1.

Competent authorities may legitimately prevent its use, nationally and at the European level.

This is not a call to increase prescriptions to support a trial[9]but to limit as much as possible the use of the drug, which is unfortunately already legitimized, by including it only in rigorous studies and well-defined therapeutic pathways. This will make it possible, on the one hand, to avoid abuse and promote pathways informed by the principle of maximum transparency and, on the other hand, to monitor the outcomes: if negative, it will be possible to prevent this practice.

Raffaele Calabrò
Tonino Cantelmi
Giuseppe Casale
Maria Grazia De Marinis
Luisa De Renzis Matilde
Leonardi Andrea
Manazza Domenico
Menorello Assunta
Morresi Claudia Navarini
Carlo Maria Petrini
Giovanna Razzano
Marcello Ricciuti
Mauro Ronco Giuliana
Ruggeri

[9] See Article 2 of the Oviedo Convention - *Primacy of Human Being.*
"The interest and good of the human being must prevail over the sole interest of societỳ or science."

Explanation of vote

We wholeheartedly endorse this paper because it is fully consistent with the CNB's 2018 opinion titled "Regarding AIFA's request on the ethicality of the use of the drug Triptorelin for the treatment of adolescents with gender dysphoria."

The new document faithfully recalls the previously stated principles and ethical requirements, merely reiterating more emphatically two of the key aspects of the 2018 opinion, namely the entirely agreeable need to strengthen the scientific evidence supporting the *off-label* use of tryptorelin in adolescents with gender dysphoria through new studies, as well as the importance of systematizing the knowledge acquired and that which will gradually be acquired, including by establishing a centralized national registry relating to data made available from routine medical practice.

However, we would like to emphasize that the new document should have strongly emphasized the merit and importance of the 2018 opinion that, in absolute discontinuity with the past, had made it possible to transform, thanks to Aifa Determination No. 21756/2019 that had implemented it, a substantially deregulated system into a rigorous protocol and a dutiful guarantee for young patients, anticipating by years what had happened only recently in many European and non-European countries. This needed to be acknowledged in this paper, along with appreciation for the work then done by the drafters of that opinion.

Lastly, it is worth making explicit, in case any misunderstanding may arise in this regard, that our shared decision not to address the issue of *gender* and to focus on the issue of *the off-label* use of tryptorelin in no way implies that the CNB-or at least we, the signatories and adherents to this Voting Statement-, are unaware of the need to be vigilant in protecting the dignity and health of *transgender* people and to oppose all forms of prejudice and discrimination against them.

Signatories:
Carlo Antonio Barone
Luisella Battaglia
Stefano Canestrari
Cinzia Caporale
Lorenzo d'Avack Silvio
Garattini
Luca Savarino

Adherents: Carla
Bernasconi
Mauro Biffoni
Guido Giustetto
Giovanni Maga

Dissenting note

I try here to explain why the cultural commitment to ethics that has always characterized my life leads me to vote against Majority Response 2024 to the Ministry of Health's question about whether to "reconsider the question of the ethicality of the use of the drug triptorelin in cases of gender dysphoria for minors."

I recognize that Response 2024 in substance does not express any explicit ethical condemnation about the use of tryptorelin as a puberty blocker, and therefore, from the standpoint of practical conclusions, the current review does not deviate too much from what was proposed in Opinion 2018. When one then considers that the U.S. state of Tennessee has recently banned by law gender transition and the use of triptorelin, that the U.S. Supreme Court is considering whether such a rule meets the expected equality criteria, and that in different forms there are winds blowing toward a ban in Europe as well, it can be said that the mediation reached constitutes an acceptable compromise, and in fact had the agreement of many of those who had signed that Opinion.

It is true that sometimes avoiding a "greater evil" (the prohibition or moral condemnation of triptorelin) in certain circumstances can be considered a "good," but this does not apply when it comes to *making an ethical* judgment, where by "ethics" we mean the sphere that determines the ultimate and supreme attitudes that guide conduct about the important and decisive issues for the self-realization and happiness of people within a framework of equality: the latter aspect that establishes the figure of a society's own level of civilization. It is this high conception of ethics that must be applied to the specific case concerning the gender dysphoria of minors, a situation in which the overriding ethical task is to give directions to foster and promote the self-realization of each and every person within a framework of real equality, a goal that is achieved by assuming an attitude of openness and toward new needs which deserve attention and listening because they pertain to the sphere of self-realization and equality and there is no reason to say that they are in themselves "wrong," except for atavistic prejudices that still lead to conceptions sometimes called "homophobic" or "transphobic" and that produce discrimination.

That outlined is the high ethics on the basis of which the Ministry has asked to "re-examine the question of the ethicality of the use of the drug triptorelin in cases of gender dysphoria for minors," and from this ethical standpoint, Response 2024 is insufficient and deficient. Instead of strongly and vigorously affirming equality and the right to self-actualization even (and especially) in the presence of gender dysphoria, as is proper to the ethical point of view, Response 2024 takes an opaque attitude about the use of triptorelin in situations of gender dysphoria, a use that is not explicitly condemned but not even approved, but merely placed in a sort of limbo tending to devalue its value. More could not be done because European drug legislation must be respected in Italy, and therefore a solution like Tennessee's is not prospective here in Europe for now. Knowing that it had to move, by necessity, within this regulatory framework, Response 2024 merely went out of its way to devalue the specific use of tryptorelin, saying that there is not enough knowledge to justify its use and that it should be reserved only for pathological and serious situations. This pathologizing of interventions about gender dysphoria does not respond to the equality proper to an ethics appropriate to high criteria of civilization. From an ethical point of view, this saying and not saying in order to achieve mediation is not good, because it does not counteract existing discrimination and does not diminish the difficulties of integration that exist. Situations of gender dysphoria involve existential difficulties that require attention and listening, but for this very reason it should be clearly stated that choices in this regard are ethically legitimate and should be made with awareness and without shame. For failing to say this, Response 2024 does not have my approval.

Having to decline specifically the points where the 2024 Response is not acceptable, I will begin by listing them in brief:

1. The Response did not confirm, as it should have, the 2018 Opinion, emphasizing its importance and positivity;
2. He took the Cass Review as a scientific point of reference, which, on the other hand, is highly criticized and in any case is not relevant to the Italian situation;
3. It severely devalued the knowledge gained so far, suggesting that we have moved superficially and with little caution;
4. He predicted (albeit in hushed tones) the need for psychiatric interventions, a point that involves a "pathologization" of the situation and forms of stigma that burden the lives of young people who instead need closeness.

I will now go through them in detail, articulating the various objections.

1. The positivity of the 2018 Opinion

In 2018, AIFA asked for an Opinion about the ethicality of the use of triptorelin for gender dysphoria in order to be able to dispense the drug within the NHS. Tryptorelin was and continues to be available for that use on the market as well (at more than €. 2,000 per cycle), and therefore the problem was to see how we could avoid discrimination between those who have the economic possibilities to access the drug and those who do not. From this perspective, the problem of the ethicality of the drug was considered, and it was seen *that prima-facie* a drug is ethical in itself, and that there is a presumption of ethicality in this regard, since such a substance is apprised to promote health (a good). In this sense, the question about the "ethicality" of a drug should be asked judiciously, because a drug can only be said to be unethical (unethical) in two different situations:

a. When the drug has adverse effects and causes harm instead of the expected benefits, as happened with thalidomide used in pregnancy, from which only a decrease in nausea was expected but instead also causes teratogenic effects:

b. When you have inherent moral objections about the very action of the drug, as happened, for example, with the "birth control pill" that blocks female fertility: an effect deemed illicit by some religious morals.

Having examined the issue on the basis of rationality and lay spirit (as it should be from a National Committee in an advanced country), the 2018 Opinion noted that neither of the two objections mentioned above held up about the use of tryptorelin, and therefore declared the ethicality of the drug's use with the (many) cautions it recommended and were then provided for in the AIFA Determination: it is a powerful drug, the use of which requires due precautions. That Opinion was groundbreaking and did so much good: it was pioneering and (rightly) very cautious, insisting quite a bit on efforts aimed at decreasing suicide risks instead of highlighting the positive aspects of interventions in this regard: those that revive a zest for life and an adequate sense of self. Even with these limitations, the 2018 Opinion enabled the overcoming of discrimination between haves and have-nots, and facilitated the path to self-actualization for the young people who requested it, increasing happiness and equality. Finally, it should also be mentioned that in fact, no severe adverse events have been reported in Italy, and this also carries considerable weight.

Instead of highlighting and enhancing the positive aspects of the 2018 Opinion, as would also have been appropriate for institutional reasons, Response 2024 mentions that Opinion only to point out how even then "in the face of potential benefits of the use of tryptorelin for the treatment of gender dysphoria in adolescents, elements of uncertainty had been identified, including the paucity of safety and efficacy studies and

The inadequacy of follow-up data of the cases treated." This, moreover, was the contention of critics who pointed out that little caution had been exercised.

In contrast, it should be noted that in 2018 there were 13 studies available to support the "Dutch protocol"-not many, but considered sufficient to justify prescribing the drug. A fact that moreover found implicit confirmation in the absence of serious adverse effects. The failure to have explicitly confirmed the goodness of the 2018 Opinion, which paved the way for the fight against discrimination on the basis of equality, is in itself a strong distance from ethical requirements, a distance that is even more pronounced when that Opinion is put in a bad light where it is noted that it would have acknowledged "the paucity of safety and efficacy studies and the insufficiency of follow-up data of treated cases" while nevertheless giving the ethical green light to the use of the drug.

2. The reference to the Cass Review

After stating that already the 2018 Opinion would have noted the insufficiency of studies about safety and efficacy, Response 2024 goes on to note that "In the years since, the relationship between the benefits and risks of tryptorelin has continued to be debated, giving rise to a major international confrontation in the scientific community, which has had varying outcomes," as it would have led some countries (such as the United Kingdom, Sweden, Finland, and Norway) to limit or even discontinue the use of tryptorelin for gender dysphoria.

One may have doubts that it was really the debate within the "scientific community" that led to the restrictions on the use of tryptorelin in those countries, and not rather the elections that changed their political orientation.

Without elaborating on this aspect (albeit an important one), Response 2024 notes that since that scientific debate called into question the "Dutch protocol" accepted by the 2018 Opinion, "The CNB considered it appropriate to revisit the specific issue referred to in the question, also in light of numerous expert hearings that represented a plurality of approaches." All of the hearings, however, "referred to a recent report known as 'The Cass Review' [... which] is not the only significant contribution within the literature on the use of tryptorelin, but it is certainly among the most relevant at this time, not least because of the heated discussion it has provoked within the scientific community."

To say that the Cass Review is a scientific contribution that is "certainly among the most relevant" partly because it provoked "heated discussion" is an improper way of crediting prominence to scientific contributions, because the Di Bella cure also provoked heated discussion, but that is not why it is scientifically creditable. In fact, many of the heated discussions are aimed at pointing out the methodological flaws and ethical limitations of the Cass Review[10]. In this regard as

[10] MCNAMARA et al (2024). *An Evidence-Based Critique of "The Cass Review" on Gender-affirming Care for Adolescent Gender Dysphoria.*
NOONE et al (2024), *Critically Appraising the Cass Report: Methodological Flaws and Unsupported Claims.*
N. DAVIE AND L. HOBBS (2024*) Cass: the good, the bad, the critical.*
C. HORTON (2024*), The Cass Review: Cis-supremacy in the UK's Approach to Healthcare for Trans Children.* International Journal of Transgender Health, 1-25.
C. HORTON and R. PEARCE (2024), *The U.K.'s Cass Review Badly Fails Trans Children.* Scientific American.
D. M. GRIJSEELS (2024), *Biological and psychosocial evidence in the Cass Review: a critical commentary*. International Journal of Transgender Health, 1-11.
FGEN (2024*). Letter from Academics Concerned About The Cass Review*.
For a continuously updated dedicated site: Dr Ruth Pearce's website.

minimum the Response should have recalled that the British Medical Association (BMA) itself on July 31, 2024 made it known that it shared concerns "about weaknesses in the methodology used in the Review e of the problems that arise in the implementation of any recommendations" and announced an articulate counter-report that is scheduled for the end of 2024[11]. Perhaps, given the authority of the source, informative objectivity and prudence would have suggested greater caution before crediting the Cass Review "among the most relevant" scientific contributions on the topic. This is also because in reality the Cass Review is a review of services offered for gender dysphoria in the British context, services that have had to deal with very specific problems that are different from ours. For example, in Great Britain there seems to have been a 4,000% increase in requests so much so that services have had to suspend operations. Here the situation is different and no "trans epidemic" is expected, as feared by some. This consideration would have been enough for Response 2024 to come to "lighten" the prominence given to the Cass Review, which was instead taken as a scientific benchmark for having argued similar theses to those asserted by Response 2024. Indeed, the conclusion on p. 196 of the Cass Review states that "in considering endocrine interventions, the high number of unknown effects about the risks/benefits in a specific individual, and the lack of robust information to help them make decisions, present a major problem in obtaining informed consent."[12]. We thus pass To the third point to consider.

3. The devaluation of the knowledge gained so far about the use of tryptorelin.

In addition to the Cass Review, "also on the basis of the hearings held, the CNB highlights the insufficiency of scientific data on the use of puberty blockers and the need to strengthen them, reiterating the need, highlighted in the scientific literature from multiple fields, for further trials. In particular, it was emphasized that it is important to clearly identify all *outcomes* (*outcomes*) of the trials, focusing on both psychological and cognitive aspects, as well as those related to physical development, and the relationships between the former and the latter."

It is surprising that Response 2024 merely reports that "insufficient scientific data on the use of puberty blockers" has been pointed out by several parties without citing at least some of the sources. If indeed the scientific data were insufficient, this would imply acknowledging that already the 2018 Opinion was sloppy in approving the use of tryptorelin, and one struggles to understand how the CNB pharmacologists who approved the Opinion at the time can now agree with the claim of the apparent "insufficiency of scientific data."

When the CNB approved the Opinion in 2018 there were 13 scientific studies available about efficacy and safety, and all were favorable. From the discussions then held in the CNB, almost everyone felt that these data were sufficient for the safe and effective use of tryptorelin, a judgment later shared by the broader scientific community (AIFA etc.). In fact, there have been no serious adverse events in Italy. Looking at the bibliographic references of the Cass Review, which goes up to 2022, we see that before 2018 there were 17 studies available (10 low quality and 7 high quality), and from 2018 to 2022 there were 33 more (13 low and 20 high

[11] Press release from BMA, "BMA to undertake an evaluation of the Cass Review on gender identity services for children and young people," Wednesday, July 31, 2024, https://www.bma.org.uk/bma-media-centre/bma-to-undertake-an-evaluation-of-the-cass-review-on-gender-identity-services-for-children-and-young-people

[12] Cass Review: 16.34 In considering endocrine interventions, the large number of unknowns regarding the risk/benefits in any one individual and the lack of robust information to help them make decisions present a major problem in obtaining informed consent (p. 196)

high). Fifteen more were published between 2023 and 2024, for a total of 55 studies. The same systematic review of the literature on which the Cass Review is based finds that van der Miesen's 2020 study[13] is of "high quality," that is, comparable to a randomized controlled trial. This study states that there is less self-harm/suicidality in those treated, with prevalences similar to youth without gender dysphoria. Basically, in untreated youth with gender dysphoria the rate is 27.2%, in those treated with triptorelin it is 12.4%, in the general population it is 11.9%, i.e., roughly equivalent. Other studies in this line are available[14], yet the majority of CNB sees the insufficiency of scientific data.

Although I am neither a pharmacologist nor a clinician, I disagree with the thesis of the absence of scientific data. As far as I have been able to investigate, the effects of the drug as such are sufficiently well known, and that what is if anything to be investigated is the effects of psychosocial therapy that makes use of the drug. It is known that any therapy presupposes values and evaluative choices, hence the uncertainties about the overall outcomes. These, however, are manageable, and in fact at least in Italy have not produced serious adverse events.

It goes without saying that further studies and in-depth studies are always welcome, and that the more knowledge the better-although we may not get to know all possible outcomes. In this regard, the majority noted the "need to fund studies of higher quality than those that have already been carried out, which do not appear adequate to the objective." The idea of proposing studies of higher quality than the current ones is certainly supportable (although sometimes it remains a wish easier said than done), but the idea that those done so far are not "adequate to the objective" is not acceptable, as if to say that so far everything has been wrong and we have to start over. To say this is to devalue the efforts of so many researchers and is against the evidence found among the many users of therapy.

4. The accentuation of psychiatric intervention.

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[13] AIR VAN DER MIESEN, TD STEENSMA, ALC DE VRIES, et al. "*Psychological Functioning in Transgender Adolescents Before and After Gender-affirmative Care Compared with Cisgender General Population Peers*," J Adolesc Health 2020; 66:699-704.

[14] - C ACHILLE, T TAGGART, NR EATON, et al. *Longitudinal Impact of Gender-affirming Endocrine Intervention on the Mental Health and Well-being of Transgender Youths: Preliminary Results*. Int J Pediatr Endocrinol. 2020;2020:8. doi: 10.1186/s13633-020-00078-2.

- M ARNOLDUSSEN, EC HOOIJMAN, BP KREUKELS, et al. *Association Between Pre-treatment IQ and Educational Achievement after Gender-affirming Treatment Including Puberty Suppression in Transgender Adolescents*. Clin Child Psychol Psychiatry. 2022;27(4):1069-1076. doi: 10.1177/13591045221091652.

- R COSTA, M DUNSFORD, E SKAGERBERG, et al. *Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria*. J Sex Med. 2015;12(11):2206-14. doi: 10.1111/jsm.13034.

- AL DE VRIES, TD STEENSMA, TA DORELEIJERS, et al. *Puberty Suppression in Adolescents with Gender Identity Disorder: a Prospective Follow-up Study.* J Sex Med. 2011;8(8):2276-83. doi: 10.1111/j.1743-6109.2010.01943.x.

- AL DE VRIES, JK MCGUIRE, TD STEENSMA, et al. *Young Adult Psychological Outcome after Puberty Suppression and Gender Reassignment*. Pediatrics. 2014;134(4):696-704. doi: 10.1542/peds.2013-2958.

- A.D. FISHER, J RISTORI, A ROMANI, et al. *Back to the Future: Is GnRHa Treatment in Transgender and Gender Diverse Adolescents Only an Extended Evaluation Phase?* J Clin Endocrinol Metab. 2024;109(6):1565-1579. doi: 10.1210/clinem/dgad729.

- DM TORDOFF, JW WANTA, A COLLIN, et al. *Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care*. JAMA Netw Open. 2022;5(2):e220978. doi: 10.1001/jamanetworkopen.2022.0978. Erratum in: JAMA Netw Open. 2022 Jul 1;5(7):e2229031. doi: 10.1001/jamanetworkopen.2022.29031.

- AIR VAN DER MIESEN, D RAAIJMAKERS, TC VAN DE GRIFT, "*You Have to Wait a Little Longer." Transgender (Mental) Health at Risk as a Consequence of Deferring Gender-Affirming Treatments During COVID-19*. Arch Sex Behav. 2020;49(5):1395-1399. doi: 10.1007/s10508-020-01754-3.

Having stated in Majority Response 2024 that tryptorelin would be given so far in the absence of sufficient data, and that it is desirable to acquire them as soon as possible, the conclusion is that "given the uncertainty about the risk/benefit ratio of blocking puberty with tryptorelin, the CNB would like to see prescriptions occur only in the context of trials promoted by the Ministry of Health." It should be noted that the proposal is made as a "wishful thinking" since current legislation allows freedom of treatment and adherence to a study cannot be made mandatory.

Regardless of whether they are involved in some kind of specific investigation, the Response recalls and recommends "that the prescription of puberty blocker [...] be done according to criteria of prudence, ensuring that patients are always evaluated and followed by a multidisciplinary team, and that they receive appropriate psychological, psychotherapeutic and possibly psychiatric intervention, which is essential before the decision to prescribe the drug, in order to assess its appropriateness." The idea that special attention should be paid "to [...] to the psychotherapeutic/psychological, and possibly psychiatric pathway" before moving on to the use of triptorelin is repeated no less than three times in just 18 lines, concluding that "the methodology just described-that is, the use of multidisciplinary clinical evaluations and the prescription of triptorelin only following the established ineffectiveness of psychological and/or psychiatric therapies-must be ensured even in the event of administrations outside of trials , that is, in the case of denial of consent to the trial or following specific clinical assessments by the physician, which should always be represented as part of the data collection." The text does not clarify whether the "established ineffectiveness of psychological and/or psychiatric therapies" prior to the prescription of triptorelin is a simple recommendation or instead a condition that "must be ensured."

It remains that, compared to the 2018 Opinion, Response 2024 comes to accentuate the importance of psychiatric intervention, something that from an ethical point of view is very problematic. Already with homosexuality, there has been a shift from moral condemnation to psychiatry of the issue, and now Response 2024 seems to imply that those of gender dysphoria are not psychological problems (even serious ones) or existential difficulties, but fall under psychiatric disorders: an aspect that is not conducive to the psycho-social situation of young people who are faced with a choice. This choice is already difficult in itself for so many different historical reasons and the uncertainties of the case, and instead of being eased as required by the ethical principles of beneficence and equality, it is stigmatized by the demand for "possibly psychiatric" intervention. This attitude results in discrimination and does not promote equality as required by ethics, which is why I do not approve of 2024's Response.

Maurizio Mori

Note of abstention

To the urging of the Ministry of Health to reconsider the ethicality of the use of the puberty-blocking drug (triptorelin) in interventions for adolescent gender dysphoria - an issue already addressed by the CNB in 2018 -, the Committee today responds by recommending that the drug be used with prudent criteria, within an integrated approach with psychosocial and possibly psychiatric components. It also recommends that the Ministry take charge of studies and research in order to strengthen the evidence about the drug's efficacy and safety. Looking at the ethical position about the use of the drug, the CNB today confirms the 2018 orientation, as Barone, Battaglia, Caporale and others rightly note in their explanation of vote. We are thus in the presence of a thoughtful pronouncement by the CNB: which I appreciated, all the more so considering the pressures and climate in which the Committee has found itself operating, amidst searing *transgender* controversies intertwined with opposition to the use of puberty blockers for gender dysphoria (also raised by parliamentary questions): in such a situation, the request to the CNB to reconsider the ethicality of tryptorelin appeared tainted by a pre-judgment of inadequacy of the 2018 opinion. However, while I agree with the substance of the final directions, the contradictory and confusing manner in which they are expressed is a source of perplexity, as I will argue below.

Equally questionable is the reconstruction of the scientific debate adduced to support the new review about tryptorelin. The CNB's Response to Ministry repeatedly refers to "lack of data," and the only document explicitly cited concerning the scientific literature is the *Cass Review.* Since the *Cass* is, according to its title, a "review of gender identity services for children and young people in the UK," it needs to be contextualized appropriately. What prompted the British government to review the service system was the rapid increase in demand (growing exponentially since 2014), so much so that it resulted in waiting lists. This is quite different from the situation in Italy, as the hearings showed. Moreover, data on the Italian situation are essential, not least to clarify in what context the new request to the CNB for a pronouncement was placed. If, as it seems, certain and complete official data were not yet available at the moment, it is essential that public authorities take prompt action in this direction.

However, since the *Cass* Review has been taken as the preferred reference point, the reservations that the *Cass* has elicited from leading international and national medical associations in the field should have been made explicit. *The British Medical Association* itself rejects the judgment of "lack of evidence" about medical treatments in gender identity services.

Moreover, *Cass* was conducted in open contrast to British service providers, the very services that the commission chaired by Hillary Cass was supposed to review. This weakness in the British document-emphasized among many other organizations by the *World Professional Association for Transgender Health (WPATH)*-is particularly troubling. Indeed, the knowledge gained in the field by service providers and the views of service users are as fundamental to shaping an appropriate service response as *evidence-based* knowledge derived from scientific research[15]. All the more so since we are dealing with issues of "gender incongruence," based on the subjective perception of the young or very young user: with respect to

[15] See the document of the Italian Psychological Association*, On the Pharmacological Suspension of Pubertal Development*, Nov. 30, 2024, where it states that not only *Evidence-Based Medicine* criteria should be used, but also *Evidence-Based Practice in Psychology* criteria, which include both empirical evidence and clinical assessment and consideration of the user's existential values (p.7).

this condition, the social response in terms of acceptance/non-acceptance of the *transgender* person plays a key role in preventing or conversely encouraging the development of the person's discomfort, stress, and suffering (which may result in "dysphoria"). For this reason, it seems to us that the indication to the Ministry in favor of a "controlled" "double-blind" clinical trial (referred to in the Response as "the *gold standard* for drug authorization") should be further explored. This is not so much a matter of authorizing a drug, since it has been in use for dozens of years in Europe and other parts of the world; nor is it a matter of simply "administering" a drug, but of psychosocial interventions integrated with medical treatment, i.e., with the drug triptorelin. In this light, the experiences (especially in Italy) of the services that have so far delivered the interventions, as well as the studies already conducted, should receive adequate attention, also and especially to set up the new studies.

With respect to the final indications, as already mentioned, I note a contradiction between the CNB's wish that "administrations should take place **only** within the framework of trials" and what is evident from the subsequent recommendations that provide for the possibility of such administrations both to those who enter trials and to those who refuse to enter them. Therefore, the adverb "only" is not only incongruous, but also ambiguous, raising relevant ethical issues: in fact, every person has the right to receive the drug he or she has been prescribed with respect to the right to health protection, and it is unethical for him or her to be denied it just because he or she does not agree to participate in a trial. In view of its specific ethical *mission*, the CNB should have, in the first instance, reaffirmed the principle of the user's freedom of choice to protect his or her rights; and then possibly invited him or her to participate in the trials, in view of their relevance to the improvement of services and public health.

It should be remembered, moreover, that in the Italian regulatory situation triptorelin is still and always prescribable, being authorized by the European and Italian drug agencies (questions to the CNB have always concerned the reimbursability of the drug by the NHS).

This CNB Response has chosen not to address the underlying *transgender* issue. Without questioning this choice, however, I believe it is necessary to mention the functioning and goals of gender identity interventions, within which the possible use of puberty blocker is envisaged. It should first be clarified, following the *American Psychological Association* - APA, that transgender people, particularly the young and very young, almost always seek professional help to "understand their gender identity" and find the most appropriate models of gender expression to cope with the complex social and relational issues related to their condition. So, interventions are mainly characterized as help in the journey of identity research. It should be pointed out that gender identification encompasses a broader scope than the body dimension, involving psychological and especially social factors. Consequently, a gender transition path will not necessarily have to involve a process of body modification. This is all the more true in the presence of subjects with "non-binary" identities, that is, who do not identify with the mutually exclusive male/female division. The discriminator in the choices of interventions lies in adherence to the subjectivity of the user, as already mentioned. In other words, it is a matter of fielding interventions of ***"validation" of the person's experience*** and orientations, offering professional abilities to listen and clarify the user's demand: ***without any prejudice with respect to the outcome***, either of gender transition with body modification (and therefore with recourse to medical treatment), or of confirmation of the sex assigned at birth, or of gender "social transition" (resorting to change of appearance, name etc. without recourse to body modification and therefore without medical treatment). In this area, definable as one of

"exploration" of gender identity, the puberty-blocking drug mainly acquires the meaning of "buying time" in identity reflection[16]. It is worth repeating: validation of the user's subjectivity without pre-judgment about his or her possible choices should be the ethical compass of services.

Still on the ethical side, the high risks of stigmatization and discrimination of transgender people should be noted. The bitterness of the confrontation over tryptorelin may lead one to believe that behind the reservations about the puberty-blocking drug and the scientific controversy is actually a hostile attitude to *transgender* people. In the perceptions of people facing gender incongruence issues, this translates into increased stigma (a danger also pointed out in some hearings). I believe that the CNB should offer reassurance on this front, committing itself to ensuring that adequate gender identity services are available with full respect for *transgender* people, protecting their right to health. This is both a commitment of high ethical value and a challenge to prejudice and discrimination; in my opinion, it should have been the first of the CNB's recommendations.

Grace Zuffa

[16] Some assessments in the *Cass Review* about puberty blockers are pregnant with bias in a troubling way. The *Cass* reports the view that puberty blockers would not fulfill the function of a "window of reflection" because the vast majority of individuals who receive the drug then confirm their choice of gender transition and subsequently switch to drug treatments. This assertion has at its basis the idea that reflection has the dignity of its name only if it leads to "rethinking," in the sense of "turning back" from the transgender perspective. In other words, a hierarchy of value is assumed among the person's possible choices. The outcome is a diminished value of the transgender person, fueling stigma.