CASE/0719/09/25

COMPLAINANT v AGB Pharma

Alleged omissions from the prescribing information for Adaflex

CASE SUMMARY

This case was in relation to the prescribing information for Adaflex (immediate-release melatonin) dated November 2023. It was alleged the prescribing information omitted "critical information on fertility warnings" from the Adaflex summary of prescribing characteristics which was misleading and a patient safety concern.

The outcome under the 2024 Code was:

Breach of Clause 2	**Bringing discredit upon, or reducing confidence in, the pharmaceutical industry**
Breach of Clause 5.1	**Failing to maintain high standards**
Breach of Clause 6.1	**Providing misleading information**
Breach of Clause 12.1	**Providing prescribing information which failed to satisfy the requirements of Clause 12.2**

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A complaint about AGB Pharma was received from a contactable complainant who described themselves as a health professional.

COMPLAINT

The complaint wording is reproduced below with some typographical errors corrected:

> "Prescribing information for Adaflex had omitted critical information on Fertility warnings from the Adaflex SPC. The prescribing information had information on pregnancy and lactation but the warning around fertility from the Adaflex SPC was not present in the prescribing information. This prescribing information was used on several promotional materials for Adaflex from November 2023 to March 2025. The SPC information on fertility for Adaflex indicates high doses of melatonin and use for longer periods than indicated may compromise fertility in humans. This fertility information omission from Adaflex prescribing information is a patient safety issue. Job code for prescribing information is UK-MEL-AGB 0133, November 2023 is date of revision of text. There are breaches of clauses 5.1 and 2 as the omission of fertility information by AGB on large

volumes of promotional material is a patient safety challenge and is misleading considering pregnancy and lactation information was present but not fertility content."

When writing to AGB Pharma, the PMCPA asked it to consider the requirements of Clauses 2, 5.1, 6.1 and 12.1 of the 2024 Code.

AGB PHARMA'S RESPONSE

The response from AGB Pharma is reproduced below:

"We are writing in response to a complaint received regarding the prescribing information for Adaflex (UK-MEL-AGB 0133), approved in November 2023. We appreciate the opportunity to provide clarification and a response to the complaint.

Commitment to Ethical Standards

At AGB Pharma, we are committed to maintaining the highest standards of ethical conduct and compliance with the ABPI Code of Practice. We strive to provide transparent, accurate and clinically relevant information to healthcare professionals to support evidence-based prescribing. Patient safety and responsible communication remain at the core of our approach.

Background and Context

The complaint relates to the alleged omission of fertility information from the Adaflex (immediate-release melatonin) prescribing information included in, or referenced by, all promotional materials used between November 2023 and March 2025.

In this context, the prescribing information accompanying these promotional materials related solely to the promoted indication of:

Insomnia in children and adolescents aged 6–17 years with ADHD, where sleep hygiene measures have been insufficient.[1]

All promotional materials used during the period described above can be accessed [URL provided], in the spirit of transparency. These materials incorporated the prescribing information in full compliance with the ABPI Code — either by embedding it directly, linking to it digitally, or referring to where it could be accessed, as appropriate to the format and context of each material.

Regarding fertility, the Adaflex Summary of Product Characteristics (SmPC) contains the following statement under 'Fertility, pregnancy and lactation':

No adequate data on the effect of melatonin on human fertility are available. Animal studies are incomplete in terms of effects on fertility. High doses of melatonin and use for longer periods than indicated may compromise fertility in humans.[1]

At the time of approval, this information was not included in the prescribing information as it reflected a theoretical and unproven risk based solely on incomplete animal data, with no supporting human evidence. Furthermore, inclusion of such text is not explicitly

required under Clause 12 of the 2024 ABPI Code of Practice, which clearly outlines the mandatory elements of prescribing information.

Addressing the Complainant's Concerns

Prescribing Information Requirements

- Clause 12.1 specifies the various elements of prescribing information that must accompany all promotional materials. It includes several key details, as well as common adverse reactions likely to be encountered in clinical practice, serious adverse reactions, and precautions and contraindications relevant to the indications being promoted.

- Fertility information is not explicitly stated as a requirement under Clause 12. Inclusion of such information is determined by the availability of supporting data and its relevance to the promoted licensed indication.

- Moreover, the Adaflex SmPC contains no additional reference to fertility elsewhere — including under 'Special Warnings and Precautions for Use' or 'Special Populations' — reinforcing that this is a theoretical precaution, not an established or clinically evidenced concern.

- Also, the ABPI Code of Practice does not require full reproduction of the SmPC. Instead, it requires inclusion of relevant and proportionate information, tailored to the promoted indication and context of use.

Context for Excluding Fertility Information

The fertility statement in the Adaflex SmPC is precautionary and based on incomplete animal data, not on any established effect in humans. During approval, it was deemed a hypothetical risk, not one of proven clinical significance.

- Evidence Base and Context: There are no human data indicating that therapeutic doses of immediate-release melatonin (up to the maximum recommended dose of 5 mg daily), as used for the promoted paediatric indication, affect fertility. The NHS likewise notes that there is no evidence suggesting melatonin (more broadly) reduces fertility in men or women.2 The fertility statement in the SmPC is therefore precautionary, based solely on limited animal data rather than any demonstrated human risk.

- Risk Context: The SmPC fertility wording refers to potential effects only at high doses or with prolonged use beyond recommended limits. These scenarios are already mitigated in the Adaflex prescribing information through explicit safeguards, including clear statements on the maximum recommended daily dose and requirements for regular review and discontinuation attempts (see wording below from the 'Dosage and Administration' section of the prescribing information).

    - *The recommended starting dose is 1-2 mg; the dose can be increased by 1 mg every week until effect up to a maximum 5 mg per*

day, independent of age; the lowest effective dose should be sought. After at least 3 months of treatment, the treatment effect should be evaluated and stopping treatment considered if no clinically relevant effect seen. The patient should be monitored at regular intervals to check that Adaflex is still the most appropriate treatment. During ongoing treatment, especially if the treatment effect is uncertain, discontinuation attempts should be made regularly e.g. once a year.

- Pregnancy and Lactation vs Fertility: The prescribing information includes precautionary statements on pregnancy and lactation because these situations involve a potential for direct exposure of the foetus or breastfed infant to melatonin. Even in the absence of extensive clinical data, such information is routinely included as a regulatory safeguard in product prescribing information to prevent inadvertent use in these populations.
    - In contrast, the fertility statement in the SmPC for Adaflex reflects a purely theoretical risk derived from incomplete animal studies, with no evidence of an effect on human fertility at therapeutic doses (up to the maximum recommended 5 mg daily). Given that Adaflex is indicated for use in a paediatric population and treatment is subject to regular review and discontinuation attempts, the fertility information was considered not clinically relevant and was therefore not included.
- Older Adolescents: While some patients at the upper end of the licensed age range may be of reproductive age, there remains no human evidence that melatonin at therapeutic doses impacts fertility. The SmPC statement reflects a theoretical precaution, and including such speculative information in the PI could detract from other clinically relevant safety guidance provided.

Given these factors, AGB Pharma determined that inclusion of fertility information was neither required under Clause 12 nor warranted based on the available evidence at the time of approval. AGB Pharma ensured that all relevant and actionable safety information was presented in accordance with ABPI Code requirements, supporting prescribers in the appropriate use of Adaflex while avoiding inclusion of non-mandatory, theoretical content that could dilute key safety guidance.

Subsequent Updates (April 2025)

In April 2025, with a refresh of promotional materials, AGB Pharma updated the prescribing information with minor administrative, formatting, and content refinements. These changes are set out below for transparency:

Section	November 2023 PI (UK-MEL-AGB-0133)	April 2025 PI (UK-AGB-ADA-0188)	Nature of Change
Heading	*UK Abbreviated Prescribing Information*	*Adaflex (Melatonin) Prescribing Information*	Updated heading

Dose / Administration	*Administration:* Oral; 30–60 minutes before bedtime.	*Dose:* starting dose 1–2 mg, 30–60 minutes before bedtime.	'30–60 minutes before bedtime' moved from Administration to Dose section for clarity
Contraindications	'Hypersensitivity to the active substance or to any of the excipients.'	'Hypersensitivity to the active substance or to any of the excipients (microcrystalline cellulose, calcium hydrogen phosphate dihydrate, magnesium stearate).'	Excipients listed explicitly
Special Warnings	'Use caution in patients with renal impairment or epilepsy.'	'Use with caution in patients with renal impairment or epilepsy.'	Minor wording tidy-up
Interactions	'tCYP1A2 inducers may decrease melatonin plasma concentration …'	'CYP1A2 inducers may decrease melatonin plasma concentration …'	Typographical error corrected
Pregnancy / Lactation / Fertility	'Pregnancy, Lactation: Not recommended during pregnancy or in women of child-bearing potential not using contraceptives, or breastfeeding.'	'Pregnancy, Lactation & Fertility: Not recommended during pregnancy or in women of child-bearing potential not using contraceptives, or breastfeeding. No adequate data on the effect of melatonin on human fertility are available … may compromise fertility in humans.'	Fertility statement added (voluntary inclusion)
Contact details	'Tel: [telephone number provided]; Email: [medical information email address provided]	'Email: [medical information email address provided]	Telephone number removed
Adverse Event Reporting	Reports to [medical information email address provided]	Reports to [pharmacovigilance email address provided]	Dedicated PV mailbox added
Administrative	Date of revision: November 2023 Job code: UK-MEL-AGB-0133	Date of revision: April 2025 Job code: UK-AGB-ADA-0188	Administrative updates

The addition of the fertility statement was made proactively and voluntarily, not as a corrective measure, but to enhance completeness and transparency of the prescribing information. This demonstrates AGB Pharma's commitment to continuous improvement and to going beyond Code obligations where appropriate.

Conclusion

In conclusion:

- There is no explicit requirement under Clause 12 to include fertility information in prescribing information.
- The fertility statement in the Adaflex SmPC is precautionary, based solely on incomplete animal data, with no human evidence demonstrating clinical relevance at therapeutic doses.
- Inclusion of fertility information is context-dependent and should reflect the relevance of the data and the promoted indication.
- Given its theoretical nature and the safeguards already included in the prescribing information (clear statements on maximum daily dose, treatment duration, and regular review), inclusion at approval was not warranted.
- The subsequent addition of the fertility statement in April 2025 was a voluntary enhancement to further strengthen transparency, not a corrective measure.
- The complainant has not provided any evidence of prescriber confusion, patient harm, or misleading practice resulting from the omission.
- The prescribing information includes, at the outset, a clear statement directing readers to refer to the Summary of Product Characteristics (SmPC) for further details before prescribing.

We therefore respectfully deny breaches of Clauses **2, 5.1, 6.1, and 12.1** of the ABPI Code. AGB Pharma has acted responsibly, proportionately, and in full alignment with both the letter and the spirit of the Code.

We trust this clarifies the rationale for our approach and addresses the concerns raised."

PANEL RULING

This case was in relation to the prescribing information for Adaflex (immediate-release melatonin) dated November 2023. The complaint alleged the prescribing information *"omitted critical information on Fertility warnings from the Adaflex SPC"* (summary of prescribing characteristics). The complainant alleged that the omission of the statement *"high doses of melatonin and use for longer periods than indicated may compromise fertility in humans"* was misleading and a patient safety concern.

The Panel noted the complainant stated that the prescribing information had appeared on several promotional materials for Adaflex from November 2023 to March 2025 but did not provide details of these materials. The Panel therefore made its ruling based on the content of the prescribing information alone.

Adaflex was indicated for the short-term treatment of jet lag in adults and insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures had been insufficient. AGB Pharma submitted that the prescribing information in question, which accompanied the promotional materials used during the period referred to by the complainant, related solely to the latter indication.

Clause 6.1 stated, among other things, that information must be accurate, unambiguous and must not mislead. Material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine.

The Panel considered whether the omission of fertility information from the prescribing information was misleading, noting that information about pregnancy and lactation was included.

The wording of Section 4.6 of the SPC in place at the time of creation of the prescribing information at issue was the version last revised December 2021, ("Fertility, pregnancy and lactation") stated:

> "Pregnancy
>
> There are no data from the use of melatonin in pregnant women. Animal studies are incomplete regarding effects on pregnancy, embryonic / fetal development, childbirth and postnatal development (see section 5.3). Exogenous melatonin readily crosses the human placenta. Considering the lack of clinical data, treatment with Adaflex is not recommended during pregnancy or in women of childbearing potential not using contraceptives.
>
> Breastfeeding
>
> Data from animal studies indicate maternal transfer of melatonin to the foetus via the placenta or in the milk. Endogenous melatonin has also been measured in breast milk from breast-feeding women, and therefore exogenous melatonin is most likely also excreted in human milk. Melatonin is therefore not recommended to breastfeeding women.
>
> Fertility
>
> No adequate data on the effect of melatonin on human fertility are available. Animal studies are incomplete in terms of effects on fertility. High doses of melatonin and use for longer periods than indicated may compromise fertility in humans."

The corresponding section of the prescribing information in question was specifically titled "PREGNANCY, LACTATION" and stated Adaflex was "Not recommended during pregnancy or in women of child-bearing potential not using contraceptives, or breastfeeding".

In the Panel's view, the prescribing information fairly reflected the relevant precautionary information for the pregnancy and breastfeeding subsections of Section 4.6 but made no reference to fertility. In this regard, the Panel considered that while there was no equivalent "not recommended" statement regarding fertility in the SPC, the fertility subsection nonetheless stated that fertility may be compromised with "high doses of melatonin and use for longer periods than indicated".

The Panel took into account AGB Pharma's submission that the fertility statement was *"a purely theoretical risk derived from incomplete animal studies, with no evidence of an effect on human fertility at therapeutic doses (up to the maximum recommended 5 mg daily)"* and that its inclusion was not relevant due to the context of the paediatric and adolescent population for which Adaflex was promoted.

In the Panel's view, however, the fertility wording in the SPC constituted relevant precautionary information, particularly in the context that treatment might be used over prolonged periods for the promoted indication of insomnia in children and adolescents with ADHD.

While the Panel acknowledged that prescribing information was abbreviated in nature and that the prescribing information at issue referred readers to the summary of product characteristics, the Panel nonetheless considered the inclusion of pregnancy and lactation information, but omission of fertility information, had the potential to imply that there were no considerations in relation to fertility, which was not so. The Panel therefore, on balance, ruled a **breach of Clause 6.1**.

Clause 12.1 required the prescribing information listed in Clause 12.2 to be provided in all promotional material for a medicine. Clause 12.2 listed the components of prescribing information. Failure to satisfy the requirements of Clause 12.2 would, therefore, be a breach of Clause 12.1.

Clause 12.2 included the requirement to include, among other things, a succinct statement of common adverse reactions likely to be encountered in clinical practice, serious adverse reactions and precautions and contraindications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the summary of product characteristics, together with a statement that prescribers should consult the summary of product characteristics in relation to other adverse reactions (12.2 v.).

The Panel considered that while Clause 12.2 did not expressly list fertility information, it did require prescribing information to include, in abbreviated form, precautions from the SPC relevant to the indications in the advertisement.

The Panel noted its comments in relation to the fertility subsection of the SPC which stated that "high doses of melatonin and use for longer periods than indicated may compromise fertility in humans". In the Panel's view, this constituted relevant precautionary information in the context of the promoted indication.

The Panel therefore considered that the prescribing information did not satisfy the requirements of Clause 12.2 and consequently ruled a **breach of Clause 12.1**.

Prescribing information was an important contributor to patient safety. The Panel considered that the production of prescribing information that omitted the precaution regarding fertility and could misleadingly imply that there were no fertility considerations for the medicine was such that AGB Pharma had failed to maintain high standards. The Panel ruled a **breach of Clause 5.1**.

The Panel noted that, prior to the receipt of this complaint, AGB Pharma had withdrawn the prescribing information at issue and updated it in April 2025 to include a statement about fertility. Nevertheless, the Panel considered that patient safety was of the utmost importance

and noted that the prescribing information at issue had been in use for approximately 16 months, from November 2023 to April 2025. As set out in the supplementary information to Clause 2, examples of activities likely to lead to a breach of Clause 2 included, among other things, prejudicing patient safety.

In the Panel's view and as per its rulings above, inclusion of pregnancy and lactation precautions but not the fertility precaution had the potential to imply that there were no considerations in relation to fertility, which was not so. It was crucial that health professionals and others could rely completely upon the industry for up-to-date and accurate information about their medicines, particularly when the omission of such information could potentially impact patient safety. The Panel ruled a **breach of Clause 2**.

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Complaint received **02 September 2025**

Case completed **22 June 2026**