CMDh

Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

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9 January 2023
EMA/CMDh/946924/2022

Subject: Clarifications related to Safety working party (SWP) response to CMDh questions regarding genotoxic medicinal products and contraception duration period

Dear Susana Almeida,

Thank you for your letter dated 15 July 2022 addressed to CMDh and SWP in which you requested clarifications related to SWP response to CMDh questions regarding genotoxic medicinal products and contraception duration period.

As some of the questions are of a scientific nature (question 1-4), the CMDh has consulted the Non-clinical Working Party (NcWP, previous SWP) on the responses. The regulatory questions (5 and 6) have been addressed by the CMDh directly.

Please find below the joint CMDh/NcWP responses, with apologies for the delay in replying:

Question 1

The SWP recommends the duration of contraception for females following cessation of treatment in case of treatment with a pure aneugenic pharmaceutical. However, there is no mention of the recommended duration of contraception for males treated with a pure aneugenic compounds. Medicines for Europe would like the EMA-SWP and CMDh to clarify the duration of contraception required for males treated with pure aneugenic compounds, and whether this information should be included in the Clinical Trial Applications and in the SmPC section 4.6 as well.

NcWP response:

In males, mitotic and meiotic divisions are primary locations for the induction of aneuploidy, while the full duration of spermatogenesis, from stem cell to seminal sperm, is a potential target for the induction of chromosomal structural aberrations and mutations (Frias S et al., 2020)

Therefore, the duration of contraception for males treated with a pure aneugenic compound should be the same as for a genotoxic compound.

Pharmaceuticals that exhibit only aneugenicity are not categorized as genotoxic pharmaceuticals. However, the same contraceptive measures should be taken as those for pharmaceuticals with

potential developmental toxicity due to genotoxicity, as spermatids and spermatozoa are the most sensitive to induction of chromosomal abnormalities by aneugenic pharmaceuticals.

The SWP paper "SWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug" (EMA/919499/2022 corr. 3*) will be amended accordingly.

Question 2

The SWP recommended for genotoxic compounds a duration of contraception of five half-lives after the last dose, plus 6/3 months for females/males, respectively. Medicines or Europe would like the EMA-SWP and CMDh to clarify the approach for calculation and presentation of the five half-lives, specifically:

(a) Most genotoxic compounds are small molecules, which have a relatively short half-life. As such, the five half-lives calculated may often result in a relatively small addition of a few days to the recommended duration of contraception of 6/3 months. Medicines for Europe would like EMA-SWP and CMDh to clarify whether there is a minimal duration of five half-lives under which this value should not be added to the 6/3 months recommended contraception period. Medicines for Europe would like to propose for genotoxic substances with a half-life of less than (or equal to) 65 hours, which calculate to 5*half-lives of less than 14 days, there would be no addition to the recommended 6 and 3 months contraception, respectively. Medicines for Europe considers that any addition below 14 days would be negligible relative to the recommended 6/3 months of contraception.

NcWP response:

In general, considerations for a safe contraception period should be based on a worst-case scenario. In other words, the length of a contraception period, calculated on the basis of the half-live of a compound, should be rounded up, and not adjusted downwards.

From a practical point of view for substances with short half-lives, the addition of only a few days to the contraception period after cessation of treatment of 6 months for females or 3 months for males is not recommended. The minimum additional time period as the starting point to be considered should be 1 month.

For substances with a 5 x $t_{1/2}$ of equal or more than 1 week (7 days) the additional time period should be rounded up to at least 1 month and increased thereafter on a per month time period. Specific examples are provided in the table below:

$t_{1/2}$	Additional time period to 6- or 3-months contraception in clinical trials or post-marketing, respectively, also given in SmPC*
5x $t_{1/2}$ < 7 days	0 days
5x $t_{1/2}$ ≥ 7 days - 28 days	1 month
5x $t_{1/2}$ > 28 days ≤ 56 days	2 months

*It is up to the decision of the doctor and/or the patient whether contraception is used for longer.

However, to give a general recommendation for the additional time period which does not need to be added to the 6 or 3 months in any case is not possible, as it depends on a range of substance-specific parameters like for example the genotoxic mechanism (*please see footnote), the tissue distribution of the substance, the protein binding, accumulation ratio, genetic polymorphism etc. Therefore, based on substance-specific properties, the additional time period for contraception that should be mentioned may be adapted.

*In humans, alkylating agents and radiation should already induce a high risk of mutations in spermatozoa produced within 1 or 2 weeks after initiation of therapy. Topoisomerase II inhibitors and possibly microtubule inhibitors produce the greatest risk at weeks 5-7 of therapy. Nucleoside analogs, antimetabolites, and bleomycin exert their mutagenic effects on spermatozoa collected at 7-10 weeks of therapy. (Meistrich, 2019)

(b) For those compounds with half-life exceeding the above proposed threshold of half-life of 65 hours/5*half-lives of 14 days, Medicines for Europe requests a clarification of how this additional should be presented in the SmPC (i.e. in full weeks or days).

NcWP response:

Expression in days might be difficult for patients to understand and to follow. For the sake of harmonisation of the respective advices given in the SmPC and to support patient compliance the approach as outline in the table above seems to be the most practical way without jeopardising patient safety.

(c) Medicines for Europe would like to confirm whether the SWP agrees that the calculation for encapsulated drugs (like liposomes) would be based on the free fraction of the genotoxic substance.

NcWP response:

The time period that should be added to the 6 months for females and 3 months for males should be the time needed for elimination of the substance from the body, for example, the time period for complete release of the substance from the liposomes plus the 5x half-live of the free fraction.

(d) Medicines for Europe would like a clarification on whether the answers to a-c above also apply to pure aneugenic compounds, for which the duration of contraception is shorter.

NcWP response:

The same considerations as outlined in the answer to a-c should be applied for pure aneugenic compounds.

Additional responses to question 2:

In the table attached to the letter of MfE additional questions were implemented in relation to the contraception period and question 2 in the letter. They are reflected below:

(e) If the half-life is expressed as a range, which value should be used (maximal value? minimal value?)

NcWP response:

As it should always be considered from a worst-case scenario, the maximum value should be used.

(f) In case the calculated five half-lives is not a full number, should the value be rounded and how?)

NcWP response:

The value should be rounded up after calculation of the 5 half-lives.

NcWP general statement for question 2:

NcWP would like to highlight that the SmPC aims to provide recommendation for safe and effective of the medicine to health care professionals. However, final decision regarding the additional time period on 6- or 3-months contraception should be taken by the doctor and/or the patient.

Question 3

In sections 3.3 and 4.3 of the SWP recommendation document it is stated that "recommendations should not apply to active substances whose mechanism of genotoxicity is known to have a threshold which is not expected to be attained in patients". It is generally accepted that aneuploidy-inducing agents exhibit a non-linear dose response curve, and have a threshold (in contrast to mutagenic or clastogenic agents), and the contraception duration for aneugenic substances is already indicated in the SWP document. Medicines for Europe would therefore ask to clarify which additional mechanisms of genotoxicity may be considered to have a threshold.

NcWP response:

There is clear evidence for direct and indirect mechanisms responsible for a threshold for genotoxicity in the public literature. One example for a direct mechanism leading to a threshold is the experimental evidence of micronucleus induction after treatment with a number of TOPO II inhibitors (Lynch et al., 2003).

Threshold dose-effect relationships can also be assumed for indirect mechanisms, leading to modifications of the genetic material at the gene, chromosome, or genome level, like decreased fidelity in DNA replication, imbalance of nucleotide pool, interaction with cell structures involved in chromosome segregation (Crebelli 2000; COM 2010). Also, exhaustion of detoxifying enzymes in the metabolism of the compound could play a role.

Only if there is clear scientific evidence for a (direct or indirect) threshold effect of the genotoxic mechanism, a safety margin for human exposure may be derived.

Question 4

Medicines for Europe would like a clarification on the practical application of the concept of "threshold which is not expected to be attained in patients". Specifically:

(a) What should be the basis for calculation of the margins (i.e. Dose? Exposure? Other?)

NcWP response:

Preferably the exposure data, like AUC-and C_{max}-values should be used as outlined in ICH M3. If not available, a dose-based comparison using the animal HED (human equivalent dose) adjusted on a body surface area according to FDA guidance and species conservation factors should be performed (FDA 2005).

(b) How should the margins be calculated and what would be considered an acceptable margin between the threshold and the patient level of exposure.

NcWP response:

The margin should be calculated by dividing the animal exposure at the NOEL (AUC or C_{max}) or the highest in-vitro no-effect concentration (NOEC) with the human exposure (AUC or C_{max}) (see also ICH M3). Differences in protein binding should be considered.

The acceptability of a specific margin for a specific product depends on the medical need and should be determined in a thorough benefit-risk assessment. Considerations should also be given to the amount and quality of data (in-vitro, animal and human data) available, the duration of human exposure, variability in the experimental data, the intra- and inter-species variation, the differences in exposure and the individual susceptibility

If possible, please provide examples of compounds that would fit into this category. Please also provide an example of how the calculation for determination of threshold and margins should be conducted and applied.

NcWP response:

Example: Moxifloxacin (Gyrase inhibitor). For considerations related to calculation please see above.

Question 5

Medicines for Europe would like a clarification on the approach to take in cases where there is no reference product registered in the country where the generic product is registered, but there are other EU countries where an originator is registered.

Example: generic product is registered in country A. No originator is registered in country A anymore, but originators are registered in other EU countries. Should section 4.6 of the SmPC of the generic product in country A be adapted to any originator in EU and which type of variation may be used? Should it be Type IB variation as the calculation was taken over from another product (see point 3.11 in CMDh meeting minutes from 25-27 January 2022): "[...] If the calculation is taken over from another product and no new calculation is required, a type IB variation is sufficient."

CMDh response:

In case a RefMP is not authorised in the MS where the generic is authorised, the calculation can be taken over from a RefMP authorised in another MS (or another product) and no new calculation is required. Submission via a type IB variation is sufficient.

Question 6

For generic drugs there is often more than one reference product registered across the EU and SmPC of these different reference products may indicate different durations of contraception. Medicines for Europe is seeking clarification from EMA-SWP and CMDh on how the proposed change in wording of section 4.6 in the SmPC should be applied in such cases.

CMDh response:

The CMDh considers this to be a theoretical question. The generic should adapt to the product information of their RefMP. MSs are exchanging information on the calculation of the contraception period. In case there are major differences between products, this would need to be further looked into and aligned.

Kind regards,

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Chair of CMDh

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