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GUIDELINE ON NON-CLINICAL AND CLINICAL DEVELOPMENT OF MEDICIAL PRODUCTS FOR THE PREVENTION OF NAUSEA AND VOMITING ASSOCIATED WITH CANCER CHEMOTHERAPY

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GUIDELINE ON NON-CLINICAL AND CLINCIAL DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF NAUSEA AND VOMITING ASSOCIATED WITH CANCER CHEMOTHERAPY

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Abbreviations

CINV Chemotherapy Induced Nausea and Vomiting

CTZ Chemoreceptor Trigger Zone

CC Complete Control: Absence of emesis and nausea (or only mild)

R Response: No emesis no use of rescue

EXECUTIVE SUMMARY

This Guideline intends to provide guidance for the evaluation of medicinal products for the prevention of nausea and vomiting associated with cancer chemotherapy and should be read in conjunction with Directive 2001/83/EC as amended and other relevant current and future EU and ICH guidelines especially those on:

- Choice of control group in clinical trials (ICH E10)
- Statistical Principles for Clinical Trials (ICH E9)
- Studies in Elderly (ICH E 7)
- Guideline on the Choice of the Non-Inferiority Margin (CPMP/EWP/2158/99)
- Points to Consider on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99)
- Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (ICH M3)

It is guidance only, but deviations should be explained and discussed in the Clinical Overviews.

1. INTRODUCTION (background)

Chemotherapy-induced nausea and vomiting (CINV) is one of the most frequently reported adverse events in patients receiving chemotherapy. If nausea and vomiting become severe, dehydration, metabolic disturbances, malnutrition or aspiration pneumonia may occur. Treatments that prevent or reduce CINV are therefore an integrated part of the supportive care of cancer patients.

The pathophysiology of CINV is complex and different chemotherapeutic agents are likely to act at least partly through different targets. Mechanisms involved include activation of the chemoreceptor trigger zone (CTZ) and/or the dorsal vagal complex directly or indirectly through stimulation of dopamine, opiate, histamine, acetylcholine, neurokinin 1 and/or serotonin type-3 ($5\text{-}HT_3$) receptors. Peripheral mechanisms are also of relevance and include injury of the gastrointestinal mucosa and stimulation of gastrointestinal neurotransmitter receptors. In addition cortical mechanisms may contribute, in particular as regards anticipatory nausea and vomiting.

2. NON-CLINICAL DEVELOPMENT

2.1 General Considerations

Taking into account the limitations in the current understanding of the underlying mechanisms involved in the development of CINV, proof-of-concept studies *in vivo* should be performed in at least one species that is considered to be adequate for the proposed mechanism (see 2.2.1 below). It is also encouraged to use different chemotherapeutic agents to induce emesis in order to characterise possible differences in the pattern of activity.

Models should be justified on the basis of good current scientific understanding. Studies investigating site of action (central and/or peripheral) are encouraged and may, for example, include known centrally acting compounds (e.g. morphine, apomorphine).

The mechanism of action in relation to “acute” and “delayed” emesis should be described in sufficient detail to discern pharmacological target(s), and, if possible, the relative importance of peripheral, e.g. gastrointestinal and central target areas, e.g. CTZ. Clinical relevance in relation to current science, and its biological properties in terms of class relationship to other molecules and known genetic variability should also be characterised.

The affinity/activity of the compound with the human target receptor should be characterised *in vitro*. Consideration should be given to the activity of the corresponding animal homologues from the species to be used in studies in vivo. An early receptor panel screen as general background information to address the specificity of the compound should be performed.

Secondary pharmacology effects in the same species background strain as used for primary screening should be used to demonstrate the within-species potential for a therapeutic window. The potential for

unwanted effects on the CNS (e.g. sedation, motor incapacitation) may need particular attention, especially for centrally acting compounds.

The experimental basis for selection of first human dose should be clearly described, and the scientific basis for inclusion/exclusion criteria and any diagnostic markers used to select the trial populations should be justified.

The possibility of a pharmacodynamic interaction between the anti-emetic drug and anti-tumour chemotherapy should be addressed. If not otherwise justified and especially for classes of compounds where non-clinical and clinical data are sparse, ex vivo cytotoxicity interaction studies in cancer cell lines supplementing studies in tumour bearing animals are recommended. Based on these data and pharmacological considerations it might not be necessary further to study this issue in clinical studies.

2.2 In-vivo Models of Chemotherapy Induces Emesis

Emesis is a reflex, which develops to different degrees in different species. Emesis comparable to man occurs only in a few animal species.

Several models addressing the physiology of emesis and the antiemetic properties of chemicals are currently described.

2.2.1 Species

The ferret and the dog are the laboratory species most widely used to address the anti emetic activity of chemicals. Increasingly, the dog is replaced with the house musk shrew (*Suncus murinus*). Other species used are pigeon, the rat, or the pig.

2.2.2 Protocols

The anti-emetic activity of a test compound can be studied in several animal species following different protocols. In general, the test compound is administered before the emetogenic challenge. Cisplatin is the emetogenic substance most frequently used, but studies using other substances like, DTIC, cyclophosphamide, or ifosfamide are encouraged.

3. CLINICAL ISSUES

3.1 Background

There are recognised predictive factors related to the risk of CINV and these can be divided into patient-related risk factors and type of chemotherapeutic agent or regimen.

The most important predictor is the emetogenic potential of the chemotherapeutic regimen defined as the intrinsic capacity of the regimen to elicit CINV. Agents and regimens are classified within a range that goes from high to low or minimal emetogenic potential. This classification is based on clinical experience and mainly refers to acute emesis, i.e. emesis within the first 24 hours.

Regarding patient characteristics, nausea and vomiting are more likely to occur in patients under 50 years of age, females, those with history of nausea and vomiting after prior chemotherapy sessions and a history of pregnancy-related nausea and vomiting. Alcohol abuse reduces the risk.

The most commonly used agents in the treatment of CINV include 5-HT_3 receptor antagonists, glucocorticosteroids, some benzodiazepines and dopamine receptor antagonists. All compounds have at least some activity against acute CINV, while currently only corticosteroids and the neurokinin 1 receptor antagonist aprepitant have well documented activity against cisplatin-induced delayed emesis.

The choice of a single or a combination antiemetic regimen, as well as the duration of treatment should be based on the emetogenic potential of the chemotherapeutic regimen.

Chemotherapy-induced nausea and vomiting can be broadly categorised as:

- *Acute*: occurring within 24 hours of therapy
- *Delayed*: occurring more than 24 hours after administration of chemotherapy and persisting for up to 5–7 days
- *Anticipatory*: occurring prior to the administration of chemotherapy and in patients with poor control of CINV during previous cycles of chemotherapy.

This classification is partly arbitrary. In the typical case of cisplatin-induced emesis, the delayed phase commences around 16-18 hours after cisplatin administration and after a period of relative quiescence, while in the case of high-dose cyclophosphamide, for example, there is no clear delineation between early and delayed emesis. Delayed emesis may in the latter case be regarded as prolonged acute emesis. Irrespective of these differences, this terminology differentiating between "acute" (≤ 24 h) and "delayed" (> 24 h) CINV has gained general acceptance in the medical community and is also accepted from a regulatory perspective.

This document intends to provide guidance on the design of clinical studies involving drug treatment of acute and delayed CINV. The role of and experience with pharmacological agents in the management of anticipatory emesis are limited and will not be covered

It should be recognised that the goal of anti-emetic therapy is to prevent nausea and vomiting, and therefore antiemetic agents should be administered before the appearance of CINV. According to current guidelines, antiemetic agents should be used to prevent CINV in all patients receiving chemotherapy regimens of high and moderate emetic risk. No regular preventive use of antiemetics is suggested for patients treated with agents of minimal risk.

3.2 Study Populations and Chemotherapy Regimes

Patients participating in efficacy studies should be well characterised with respect to covariates of importance for CINV, including the response to antiemetic therapy in previous chemotherapy cycles. In addition to demographic characteristics (age, sex, ethnicity), type of cancer (adjuvant, advanced/metastatic), Karnofsky performance status and history of alcohol consumption should be detailed.

Poorly controlled nausea and vomiting in previous chemotherapy cycles increases the likelihood of CINV. Chemotherapy-naïve patients should therefore be studied and/or analysed separately from chemotherapy-experienced patients. Those latter patients should be categorised into responders and non-responders to previous antiemetic treatment. The term "refractory CINV" refers to emesis which occurs despite adequate antiemetic prevention and rescue.

Patients receiving multi-day chemotherapy are at risk for CINV on days of and subsequent to chemotherapy. The period at risk for CINV after the end of a multi-day regimen depends on the specific regimen and mainly on the emetogenic potential of the chemotherapy agents administered late in the regimen.

With respect to the emetogenic potential of chemotherapeutic regimens, several classifications have been developed. Although it may be sufficient in clinical practice to differentiate between high, moderate and mild emetogenic potential, scales with more categories are frequently used in clinical trials. One of these is the original Hesketh Scale, with five different categories and a specific algorithm to determine the emetic potential of a chemotherapeutic combination, mainly according to the most emetogenic agent in the combination. This instrument was recently (2005) modified and now encompasses also oral chemotherapeutic agents and uses a four-level categorisation as regards emetogenic risk. As indicated previously, these scales are more relevant for acute than delayed CINV.

From a regulatory perspective it is acceptable to use a restricted number of predefined regimens falling within the same emetogenic risk category for the documentation of the treatment effects as regards acute CINV.

As regards delayed CINV, the regulatory experience is limited and the underlying pathophysiology poorly defined with respect to putative differences related to type of chemotherapy. For a non-restricted indication, it is currently recommended that activity should be documented separately against delayed CINV caused by highly emetogenic cisplatin and non-cisplatin based regimens. It is advisable to focus on one (or a few very similar) non-cisplatin based regimen with well-documented and clinically significant delayed CINV. Non-clinical mechanistic data may be used to provide support for the possibility to extrapolate.

3.3 Methods to Assess Efficacy

The aim of antiemetic therapy is to prevent nausea and vomiting. Emesis has been the most frequently used primary end-point in studies with antiemetic agents. It can be measured by emetic episodes (vomiting and/or retches/dry heaves) by means of direct observation at the clinical site during first

hours or, preferably, by means of a daily diary completed by the patient. Assessment of nausea may be more difficult due to its subjective nature and nausea has been used as a secondary endpoint in many clinical trials. Both duration and intensity by means of visual analogue scales or ordinal scores should be assessed.

Responder analysis provides a meaningful way to assess efficacy. A patient may be defined as a responder if no emetic episode occurs. Control of nausea is usually less successful than control of vomiting. A patient may be considered as a responder if no, or only mild nausea is reported. Use of rescue medication or withdrawal should be considered as treatment failures.

Due to the relevance of both vomiting and nausea, the percentage of patients with complete control (CC), meaning absence of emesis and nausea (or only mild) is a meaningful end point. No emesis and no use of rescue constitute an alternative and acceptable definition of response (R).

Covariate information for known influential covariates in CINV should be prespecified and included in the statistical model to control for potential imbalances (Points to Consider on Adjustment for baseline Covariates, CPMP/EWP/2863/99). If chemotherapy experienced patients are included, stratification by response to prior anti-emetic therapy should be considered.

The Functional Living Index of Emesis (FLIE) is an accepted questionnaire specifically designed to assess the impact of chemotherapy-induced nausea and vomiting on patients' daily function and may provide meaningful supportive evidence of activity.

The risk period for CINV after receiving chemotherapy of high and moderate emetic risk usually lasts for 4-7 days and efficacy data are needed for the whole period at risk after receiving chemotherapy.

Depending on the objectives of the study, CC or R during the first 24 hours after chemotherapy or for the full period at risk, e.g. 5 days may be used as primary end point for main efficacy trials. Also if the aim is to improve acute CINV, results for the full period at risk should be reported and at least non-inferiority demonstrated. The efficacy of any product should be evaluated throughout multiple cycles.

Control during the first chemotherapy cycle is an important predictor for CINV in subsequent cycles. In order to provide non-confounded data on sustained activity, re-randomisation prior to the second cycle of chemotherapy should be considered in at least one confirmatory study. This especially refers to new classes of compounds.

Depending on the objectives of the trial, secondary efficacy parameters may include:

- Proportion of subjects with CC or R during the acute phase (0-24 hours) and the delayed phase (25-120[*] hours)
- Time to treatment failure (based on time to first emetic episode or time to rescue medication, whichever occurs first)
- Number of subjects with rescue medication
- Proportion of subjects with complete or almost complete control of nausea, evaluated during acute phase (0-24h), delayed (25-120h) and 0-120 h
- Severity of nausea measured daily and overall 0-120h by means of a visual analogue scales or a Likert scale
- Peak nausea score
- Subjects global satisfaction with antiemetic therapy daily for the 0-120-hour interval by means of a visual analogue scales or a Likert scale
- The modified FLIE questionnaire may be used to assess effects during the first 24-hour time period and the standard FLIE for the 24 to 96 hour time period.

[*] In these examples the period at risk is assumed to be 120 hours, but, as stated elsewhere, this period should be defined in relation to the administered chemotherapy regimen

- Proportion of subjects with CC or R during the acute phase (0-24 hours) and the delayed phase (25-120* hours)
- Time to treatment failure (based on time to first emetic episode or time to rescue medication, whichever occurs first)
- Number of subjects with rescue medication
- Proportion of subjects with complete or almost complete control of nausea, evaluated during acute phase (0-24 hours), delayed (25-120 hours) and 0-120 hours
- Severity of nausea measured daily and overall 0-120 hours by means of a visual analogue scales or a Likert scale
- Peak nausea score
- Subjects global satisfaction with antiemetic therapy daily for the 0-120-hour interval by means of a visual analogue scales or a Likert scale
- The modified FLIE questionnaire may be used to assess effects during the first 24-hour time period and the standard FLIE for the 24 to 96 hour time period.

As indicated above the definition of "acute" and "delayed" is arbitrary, and other definitions are acceptable, especially if based on the understanding of underlying pathophysiology, but data should in addition be reported in accordance with the standard definition. If claims related to secondary endpoints are foreseen, a testing strategy should be in place avoiding multiplicity issues (CPMP Points to Consider on Multiplicity Issues in Clinical Trials, CPMP/EWP/908/99).

3.4 Strategy and Design of Clinical Trials

3.4.1 Pharmacokinetics

It is expected that the pharmacokinetics of the experimental compound is documented in accordance with relevant guidelines. Initial PK studies should be conducted in healthy volunteers.

The problems related to the conduct of interaction studies with cytotoxic compounds are recognised, but specific interaction studies are expected if there is a mechanistic potential for such interactions. In addition, it is recommended that sampling (PK and/or dynamic data, such as absolute neutrophil count of relevance for the cytotoxic compounds) is carried out within efficacy/safety studies in order to provide further information as regards potential or identified interactions.

3.4.2 Therapeutic Exploratory Studies

In order to identify proper doses and posologies for confirmatory studies, dose and schedule finding studies should aim at defining a dose range and posologies where relevant clinical activity is shown. The design of these studies should be parallel-group, fixed dose and schedule, double-blind controlled trials with at least 3 different dosages of the test treatment. Pharmacokinetics and receptor occupancy data may facilitate the interpretation of study data.

In exploratory studies it may be useful to use emesis as primary measure of activity and consider nausea-related variables as secondary end points.

Early monotherapy studies may be conducted in patients with regimens of rather low emetogenic potential in order to define active dosages to bring forward to studies in patients undergoing more emetogenic therapy. Use of placebo alone is not recommended in case of chemotherapy regimens with high or moderate emetogenic potential.

In most cases, at least if the aim is to document activity in cases of chemotherapies of high emetogenic potential, there will be a need to combine compounds to obtain satisfactory results. Randomised exploratory, add-on or substitution trials (see below) using a generally recognised regimen as reference are recommended in order to optimise the posology of the experimental compound.

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* In these examples the period at risk is assumed to be 120 hours, but, as stated elsewhere, this period should be defined in relation to the administered chemotherapy regimen

3.4.3 Main efficacy Studies

The antiemetic efficacy of a new product should be evaluated in the first cycle and during subsequent treatment cycles in order to assess the maintenance of the effect. At least one trial applying re-randomisation prior to next cycle is recommended (see 3.2).

The reference product or regimen should be evidence-based and used in accordance with recognised and updated treatment guidelines taking into account the emetogenic risk both in the acute and the delayed phase. Especially with respect to delayed cisplatin CINV and "standard therapy" it is of importance to consider the proven activity of the reference.

If it cannot be excluded with reasonable certainty (see 2.1) that the experimental compound may show a relevant dynamic interaction with chemotherapy as regards anti-tumour activity, the confirmatory studies programme should be planned to assess that possibility. Therefore a defined chemotherapy regimen in a homogenous population of patients with a defined and chemosensitive disease should be chosen and the number of patients should be justified also from an anti-tumour activity perspective. Response rate is an acceptable measure of anti-tumour activity and acceptance criteria should be prespecified.

Clinical trials should be parallel-group, double-blind, randomised and well controlled. With respect to monotherapy studies, superiority or non-inferiority compared with an accepted active reference should be demonstrated. If the new product is to be used in a combination, the study may assess whether add-on of the new agent to standard therapy is superior to standard therapy plus placebo in non-responders to standard antiemetics in previous cycles or in chemotherapy naïve patients who receive highly emetogenic agents. Substitution within a recognised regimen (AB) is an alternative. In this case and for non-inferiority studies, the contribution of the substituted element (B) to the activity of the standard regimen (AB) must be well defined in order to allow for a meaningful comparison with the experimental regimen (AX) and to set acceptance limits (Guideline on the Choice of the Non-Inferiority Margin CPMP/EWP/2158/99). If the activity of B cannot be defined based on historical data and if the activity of A alone cannot be studied within the trial (A vs. AB vs. AX), "no difference results" are non-interpretable.

If CC or R is selected as primary measure of efficacy, consistency is expected as regards secondary endpoints; in case of R especially control of nausea. The confounding effect of use of rescue, however, has to be taken into account.

In cases where relevant add-on activity to a standard regimen has been demonstrated in patients undergoing highly emetogenic chemotherapy, it cannot be postulated that the experimental compound will show relevant add-on activity in case of moderately emetogenic therapy, even if the same standard regimen is used also in these patients. In order to support claims, studies specifically addressing this issue are expected. If, however, at least non-inferior activity has been shown in a substitution study in case of highly emetogenic therapy and the use of the standard regimen is well documented also in moderately emetogenic chemotherapy, extrapolation as regards activity might be feasible, but should be justified.

3.4.4 Studies in Special Populations

In accordance with general guidelines and especially as cancer is a disease of the elderly, a sufficient number of elderly patients should be included in the confirmatory studies to provide a firm basis for the assessment of safety and efficacy. The conduct of studies that include patients above the age of 75 is encouraged. The outlines of a paediatric studies programme should be available at the time of submission for marketing approval.

Women are at higher risk of CINV and it is therefore of relevance to design the confirmatory studies programme taking this into account so that a sufficiently high number of women and men are enrolled.

3.5 Clinical Safety Evaluation

It is difficult to fully define the safety profile of an antiemetic compound when used in conjunction with chemotherapy. Therefore, it is of special importance to assess safety data derived from the use of the product in other conditions, such as postoperative nausea and vomiting, as well as from healthy volunteers in clinical pharmacology studies. Non-clinical data should be used to guide the safety assessment.