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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

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

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Any comments to this Guideline should be sent to the EMEA EWP Secretariat (Fax: +44 20 74 18 86 13) by end of August 2005

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

This Guideline is intended to provide guidance for the evaluation of medicinal products for the treatment 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)

➢ Choice of Non-inferiority Margin, Points to Consider (CPMP/EWP 2158/99)

➢ 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

Chemotherapy-induced nausea and vomiting (CINV) is the most frequently reported adverse event 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 not well understood and different chemotherapeutic agents are likely to act at least partly through different targets. Mechanisms involved include activation of the chemotherapy receptor trigger zone (CTZ) directly or indirectly through stimulation of dopamine, opiate, histamine, acetylcholine, neurokinin 1 and/or serotonin type-3 (5-HT$_3$) receptors. Peripheral mechanisms are also of relevance and include injury of the gastrointestinal mucosa and stimulation of gastrointestinal neurotransmittor receptors. In addition cortical and vestibular mechanisms may contribute.

2. NON-CLINICAL DEVELOPMENT

2.1 General Considerations

Taking into account the deficiencies in the current understanding of the underlying mechanisms involved in the development of CINV, whenever possible, proof-of-concept studies *in vivo* should be performed in more than one animal model that is considered to be adequate for the proposed mechanism. It is also advisable 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. Comparison to other compounds with known effect on the intended mechanism should be performed if applicable. Since the intended clinical use would be over repeated cycles, it is important to demonstrate the persistence of the treatment effect.

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

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relation to current science, and its biological properties in terms of class relationship to other molecules and known genetic variability should also be characterised.

In vitro studies should be performed to characterise the pharmaceutical's interaction with the human target. Consideration should be given to the use of animal homologues from the species to be used for *in vivo* studies. Selectivity data comparing interaction with human proteins closely related to the target should also be presented when applicable. Early panel screens are also encouraged as general background information for safety assessment of clinical trials.

Secondary pharmacology effects in same species background strain used for primary screening should be sought to demonstrate the within-species potential for a therapeutic window. The potential for sedation, motor incapacitation and cognitive disturbances may need particular attention.

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 possible pharmacodynamic interactions between the anti-emetic drug and the anti-tumour chemotherapy should be adequately addressed. Especially for pharmacological classes of compounds where non-clinical and clinical data are sparse, it is advisable to conduct interaction studies *in vitro* and in tumour bearing animals. 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-induced 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 dog and the ferret are the laboratory species more currently used to address the anti emetic activity of chemicals. Other species used are the pigeon, the rat, -the pig, or the house musk shrew (*Suncus murinus*).

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 recommended.

The standard approach is the drug-induced emesis in several species (dog, pig, ferret, house musk shrew or pigeon)

Other approaches are also described, such as drug-induced pica in the rat, foot tapping in gerbils.

3. CLINICAL ISSUES

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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 relates to acute emesis, i.e. emesis within the first 24 hours.

Regarding patient characteristics, nausea and vomiting are more likely to occur in patient 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 are 5-HT$_3$ receptor antagonists, glucocorticosteroids and dopamine receptor antagonists. Recently, a new antiemetic agent (aprepitant), an antagonist of the neurokinin 1 (NK1) receptor, was marketed for the prevention of CINV. All compounds have at least some activity against acute CINV, while currently only corticosteroids and 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*: beginning more than 24 hours after therapy 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 and in the typical case of cisplatin-induced emesis, the delayed phase commence around 16-18 hours after cisplatin administration and after a period of relative quiescence, while in the case of high-dose cyclophosphamide, e.g., there is no clear delineation between early and late emesis.

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 in this PtC

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 agents 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 Regimens

The patients 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, 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 while on chemotherapy and delayed emesis. The period at risk for delayed 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 of commonly used agents have been developed. Although it may be sufficient in clinical practice to differentiate between high, moderate and mild emetogenic potential, in clinical trials it is advisable to refine the characterisation by the use of a system with more categories. One of these is the 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. Several modifications and amendments to the original classification have been published and they may be used if generally recognised by the scientific community.

As indicated previously, these scales are more relevant for acute than delayed CINV and from a regulatory perspective it is acceptable to use different regimens falling within the same category for the documentation of the treatment effects as regards acute CINV.

For delayed emesis, however, the experience is currently too limited and the underlying pathophysiology too ill defined to support extrapolation, e.g. from effects on cisplatin induced delayed CINV to other compounds associated with significant delayed emesis. It is therefore recommended to use similar chemotherapeutic regimens within a specific study if the aim is to document activity against delayed CINV and not to base inclusion solely on, e.g. the Hesketh classification. For a non-restricted indication, relevant activity should also be documented for non-related regimens. 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 the appearance of nausea and vomiting. Emesis or vomiting has been the most frequently used primary end-point in studies with new antiemetic agents. It can be measured by the number of emetic episodes (vomiting and/or retching) by means of direct observation at the clinical site during first hours or, preferably, by means of a daily diary completed by the patient. The assessment of nausea may be more difficult due to its subjective nature and nausea has been considered as a secondary end-point in many clinical trials. Both frequency by means of a diary and the intensity by means of visual analogue scales or ordinal scores should be considered.

Definition of responders is a meaningful way to assess efficacy. A patient may be defined as a responder if no emetic episode (vomiting or retching) 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 are reported. Despite the limited activity of rescue medication, 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, although it coincides very much with control of nausea.

The risk period for CINV after receiving chemotherapy of high and moderate emetic risk last for at least 4-5 days and efficacy data are needed for the whole period of risk after receiving

chemotherapy. The incidence of nausea and vomiting during the acute phase is probably a predictor of the incidence of delayed CINV.

Depending on the objectives of the study CC during the first 24 hours after chemotherapy or for 5 days may be used as primary end point for main efficacy trials. 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 during the acute phase (0-24 hours), the delayed phase (25-120 hours) or during the full risk period.

- Proportion of subjects with *major* control of emesis (≤ 2 emetic episodes), *minor* (3-5 emetic episodes) and *failure* (>5); evaluated during acute phase (0-24h), delayed (25-120h) and for overall 0-120 h interval after chemotherapy.

- Proportion of subjects with complete or almost complete control of nausea, evaluated during acute phase (0-24h), delayed (25-120h) and for overall 0-120 h interval after chemotherapy

- 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

- Severity of nausea measured daily and overall 0-120h by means of a visual analogue scales or a Likert scale

- Subjects global satisfaction with antiemetic therapy daily for the 0-120 h interval by means of a visual analogue scales or a Likert scale

- An accepted questionnaire specifically designed to assess the impact of chemotherapy-induced nausea and vomiting on patients' daily function is the Functional Living Index of Emesis (FLIE). 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. In general, all secondary variables should be assessed at first cycle and at the overall chemotherapy treatment. If claims related to secondary endpoints are foreseen, a testing strategy should be in place avoiding multiplicity issues.

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.

The specific problems related to the conduct of interaction studies with cytotoxic compounds are recognised. Whenever there is a mechanistic potential for a kinetic interaction with a cytotoxic compound in a regimen to be administered, it is recommended that sampling (kinetic and/or dynamic data such as ANC) is carried out within efficacy/safety studies in order to provide some additional data that may be used to elucidate the situation.

For compounds metabolised and/or excreted by the liver, it is also expected that the number of patients with liver metastases and hyperbilirubinemia is sufficient for an assessment of potential effects on exposure, preferably prior to the initiation of confirmatory studies.

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 in monotherapy. The design of these studies should be parallel, fixed dose and schedule, double-blind with at least 3 different dosages. 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 studies may be conducted in patients with regimens of rather low emetogenic potential. However, exploratory studies in patients receiving highly emetogenic therapy will have to be conducted prior to confirmatory trials in such patients. 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 using a generally recognised regimen as reference are recommended. The benefits of the experimental compound as part of a regimen when administered for more than one day in order to control delayed emesis should be investigated.

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 treatment guidelines taking into account the emetogenic risk both in the acute and the delayed phase. For highly and moderately emetogenic regimens, antiemetic therapy should start before administration of chemotherapy, covering the acute phase and in many cases continued on days 2 through 4 after completion of chemotherapy in order to cover the period of delayed CINV.

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

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. 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, i.e. the delta (ref. PtC on the choice of non-inferiority margin). Add-on studies may be conducted in non-

responders to standard antiemetics in previous cycle or in chemotherapy naive patients who receive highly emetogenic agents.

As non-inferiority trials are likely to be the rule, studies in patients receiving highly emetogenic regimens are preferred and efforts should be undertaken to maximise the ability of the trial to detect differences in case they exist (i.e. high proportion of women included, exclusion of patients with alcohol abuse antecedents, use of single dose chemotherapy regimens,..). If CC is selected as primary measure of efficacy, consistency is expected, e.g. with respect to control of emesis. With respect to delayed emesis and "standard therapy" it is of special importance to consider the proven activity of the reference in this situation.

Clinical trials in patients with moderately emetogenic regimens are also recommended in order to provide supportive evidence of efficacy and, as appropriate, further information about potential pharmacokinetic interactions. For compounds previously studied as add-on to standard therapy, this is required in order to provide data showing relevant add-on effect also in case of moderately emetogenic regimens.

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. If not otherwise justified, at least the outlines of a paediatric studies programme should be available at the time of submission for marketing approval.

3.5   Clinical Safety Evaluation

It is difficult to 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.