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NOTE FOR GUIDANCE ON EVALUATION OF ANTICANCER MEDICINAL PRODUCTS IN MAN

ADDENDUM ON PAEDIATRIC ONCOLOGY

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This Addendum is part of the NfG on evaluation of anticancer medicinal products in man (CPMP/EWP/205/95, rev. 2), which was adopted July 2003.

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ADDENDUM ON PAEDIATRIC ONCOLOGY

1. INTRODUCTION

Childhood malignancies include all paediatric cancers which are specific to children, (e.g., nephroblastoma) and other malignancies that are not unique to the paediatric population (e.g., osteosarcoma, acute leukaemias malignant lymphomas and brain tumours). As stated in the ICH note for guidance E11 on the Clinical Investigation of Medicinal Products in the Paediatric Population, *"Paediatric patients should be given medicines that have been appropriately evaluated for their use. (...) Justification for the timing and the approach to the clinical program needs to be clearly addressed with regulatory authorities at an early stage and then periodically during the medicinal product development process"*.

The Note for Guidance on evaluation of anticancer medicinal products in man (CPMP/EWP/205/95) addresses general regulatory aspects in anticancer drug development and this guideline is generally also applicable for drugs intended for childhood malignancies. The aim of this *addendum* is to complement the current guideline with specific regulatory requirements related to paediatric oncology and to provide more specific information on the design and conduct of phase I trials in paediatric cancer patients.

The *addendum* should be read in conjunction with:

- ICH E11. Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99). Note for guidance on the preclinical evaluation of anticancer medicinal products (CPMP/SWP/997/96).
- The Note for Guidance on evaluation of anticancer medicinal products in man (CPMP/EWP/205/95).
- ICH M3 Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (CPMP/ICH/268/95, modification).
- Smith, M., M. Bernstein, et al. (1998) "Conduct of Phase I trials in Children With Cancer." *J Clin Oncol* **16**(3): 966-78.

2. GENERAL ASPECTS OF CLINICAL DEVELOPMENT IN THE PAEDIATRIC POPULATION

The majority of childhood malignancies consists of rare conditions that uniquely affect this population. A large percentage of paediatric patients in Europe affected by these conditions are treated within the context of clinical trials conducted by co-operative groups. It is important that promising new agents are made available at an early stage in their development so that their use can be studied for such conditions without unnecessary delays in the start of evaluation in the paediatric population.

Considering the low incidence of cancer in childhood and the high cure rate for some paediatric cancers, albeit with of lasting secondary effects, it is acknowledged that many more investigational agents are evaluated in adult patients in comparison to the number of agents that can be evaluated in children. Different agents will have different priority for evaluation in the paediatric population. However, due to the serious or life-threatening nature of many paediatric cancers, the identification of products that represent a potentially important advance in therapy prompts the need for urgent and early initiation of paediatric studies. In such cases, clinical development should begin early in the paediatric population, following assessment of initial safety data and reasonable evidence of potential benefit. Also negative effects of anticancer drugs on the developing human body can cause serious "late effects" in

survivors of childhood cancer. This further stresses the need to develop more specific anticancer drugs with less (long term) side effects and the need for long term follow-up of cancer survivors and pharmacovigilance.

Sponsors need to address the timing and the approach to the development of anticancer agents in childhood malignancies at an early stage of development and then periodically during the development process. It is strongly recommended that sponsors seek advice from established paediatric oncology co-operative groups and regulatory authorities, concerning the optimal timing for conducting trials in paediatric patients or for making the product available to other entities, such as co-operative groups or children's cancer research centres.

Pre-clinical data from expression profiling cell line model systems can show principle activity and more important, can show with high predictive value the inactivity. Such data are valuable in identifying and prioritising agents that warrant investigation in children. Other validated model systems such as xenografts of paediatric tumours can be also useful in this respect. For example, a number of cell line and xenograft models have been developed that apply to rhabdomyosarcoma, acute lymphoblastic leukaemia, paediatric brain tumours, neuroblastoma and osteosarcoma and they can be used to predict and study anti-tumour activity of various agents.

- Sponsors should carry out extensive testing of new agents in predictive model systems of paediatric tumours at an early stage of pre-clinical development. (refer also to Note for guidance on Pre-Clinical Evaluation of Anticancer Medicinal Products CPMP/SWP/997/96).

  Where appropriate, a package of pre-clinical analyses of predictive tumours should consider analyses to ascertain the presence of the molecular target for the drug in paediatric tumours (expression profiling, immunohistochemistry, etc.), *in-vitro* interference assays to show tumour dependency of the target; analyses to validate the drug target interaction *in vitro* by cell line studies aimed at cytotoxicity and relevant biological endpoints; testing the drug in xenograft models of paediatric tumours, where justified.

For agents that are also being evaluated in adult patients, agents that have completed phase I trials in adults and that have shown activity against paediatric tumours in pre-clinical systems or have shown promising anti-tumour activity against relevant adult tumours should be made available for evaluation in children within 6 to 9 months of completion of adult phase I trials.

For agents specific to a paediatric tumour that will not be evaluated in adults, phase I studies in the paediatric population should start as soon as clinical development can be initiated.

Factors to be considered for prioritisation of agents include: adequate activity / toxicity in preclinical models, novel mechanism of action, favourable attributes for analogues and a favourable drug-resistance profile. It should be noted however, that preclinical drug resistance in general does not have a strong correlation with clinical drug resistance, particularly in patients that have been heavily pretreated.

Sponsors should seek advice on setting priorities for the development of anticancer agents in childhood malignancies from established international paediatric oncology co-operative groups and regulatory authorities.

3. REQUIREMENTS FOR REGISTRATION

- The requirements for Authorisation as set in the Note for Guidance on the Evaluation of Anticancer Medicinal Products in man are generally applicable for a registration of an agent in paediatric cancer including the Marketing Authorisation under exceptional circumstances.

A marketing authorisation application for adult use should contain information on any past, ongoing or planned development in paediatric oncology. Sponsors should include a comprehensive overview on any testing of the agent for activity against pre-clinical model systems of paediatric tumours. The information should describe instances where the sponsor has made the medicinal product available to other entities, such as co-operative groups or children's cancer research centres, where this has led to studies in the paediatric population. Absence of paediatric oncology development (including pre-clinical testing) should be justified.

In the case of malignancies that occur both in the adult and paediatric population having the same biological or clinical characteristics, and where the clinical development relies mainly on adult data, it is important to clarify with the regulatory authorities the requirements for extending approved use of the agent to paediatric patients affected by the same cancer, such as pharmacokinetics, dosing and safety. Factors to be considered include possible differences between childhood and adult tumours with respect to geno/phenotypic properties of the tumours, preclinical activity of the new agent, human pharmacokinetics/pharmacodynamics as regards tumour markers, available treatment options. The pharmacokinetic profile constitutes the basis for the dose recommendations to different age groups within the paediatric population and thus it is important to include sufficient number of patients reflecting the age range for which approval will be sought. Other factors, such as e.g. weight, might be useful to further optimise the initial dosing regimen. It is recommended to measure markers of efficacy and toxicity to gather as much information as possible regarding the concentration-response/toxicity relationship.

Data requirements and the timing of paediatric development for those situations where pharmacokinetic studies in the paediatric population are deemed sufficient to support an extrapolation of the demonstrated benefit in adults to the paediatric population, should be discussed with the regulatory authorities.

In some situations ("exceptional circumstances") it cannot reasonably be expected that comprehensive clinical efficacy and safety data are provided by the applicant at the time of submission. For instance, it may be unrealistic to expect long-term results in childhood cancer survivors to be available at the time of submission. In these situations, it is essential to discuss at an early stage with regulatory authorities the possibility of submitting interim clinical results in paediatric patients, where necessary combined with post-authorisation commitments to complement the data submitted.

4. DESIGN OF PHASE I TRIALS IN CHILDREN WITH CANCER

A phase I trial from the child’s point of view has to be a potentially active treatment, not only an evaluation of toxicity. The leading idea of the trial design should be that children are given drugs on phase I studies with therapeutic intent.

Eligibility Criteria

Eligibility criteria for phase I trials should ensure that patients have an adequate physiologic status, so that the organ-specific toxicities observed in phase I trials can be attributed to the agents under investigation, and can be identified and differentiated from underlying organ dysfunction.

- The adequacy of kidney and liver function is especially important, since inadequate hepatic or renal function may impair drug clearance, which may lead to excessive toxicity and to the determination of an inappropriately low Maximum Tolerated Dose (MTD);

- Patients with solid tumours should have adequate bone marrow function to permit evaluation of haematopoietic toxicity.
- Patients should have adequate pulmonary and cardiac function
- Patients should have recovered from the toxicities of previous therapy and should not be receiving concurrent anticancer therapy (unless foreseen in the protocol, for example, in combination phase I studies);
- Patients should have adequate performance status measured using appropriate paediatric performance status scales (e.g., Lansky play-performance $\geq$ 50, see Appendix 1).

Starting Dose and Subsequent Dose Levels

Doses for paediatric patients may be defined in mg/kg. A variety of dose-escalations strategies have been evaluated with the goal to minimize the number of dose levels required to reach the MTD and can be used. However, the MTD may not always be the goal. Particularly for biological agents and other agents that have targets in the tissue surrounding the tumour, a biologically effective dose may be the goal for the Phase II dose. It may not be necessary to determine a maximally tolerated dose for phase I studies but rather to determine a biologically effective dose and a clinically active dose.

- The common practice for cytotoxic drugs in paediatric phase I trials is to use a starting dose that is 80% of the MTD determined in adult patients who have received significant prior therapy, and then to escalate the dose in 20-30% increments in successive cohorts of patients with no intra-patient dose escalation generally permitted. This strategy presumes that children will have a similar or higher threshold for toxicity in comparison to adults and aims to keep the number of children required for phase I trials as low as possible.
- If there is no adult MTD and no unacceptable individual toxicity then intra-patient dose escalation should be performed so that the child gets the chance to receive an effective dose. The expectation to see individual efficacy is more important than the chance to report on cumulative toxicity.
- The dose-limiting toxicities (DLT) may differ across patients which are more or less heavily pre-treated and where appropriate, exploration of this potential difference should be considered.
- Generally only the first course of therapy is used to define DLT. However, patients are generally able to continue on study for multiple treatment courses in the absence of progressive disease, provided that patients are receiving overall objective benefit from treatment (e.g., pain relief, prolonged disease stabilisation, or response). Sponsors must ensure that continuation of treatment is made possible as long patients as are receiving overall objective benefit from treatment and further treatment is deemed appropriate, according to the physician's judgement. Also data from patients who receive multiple courses can provide preliminary evidence for cumulative toxicity.

Clinical pharmacology

Pharmacokinetic data obtained in paediatric phase I trials allow comparisons of systemic exposure between adult and paediatric patients. In Phase I/II, evaluation of the pharmacokinetics in the paediatric population is should be considered. Methods are available for analysis of drug concentrations in small plasma volumes allowing pharmacokinetic evaluation also in small children. In particular, pharmacokinetic data should be used to identify age-groups with dissimilar exposure and dose need. The inter-individual variability as well as individual data should be presented to enable identification of sub-groups of patients for which alternative dosing regimens are needed. An estimate of the intra-patient variability

is helpful, since large variability reduces the possibility of successful dose adjustments between cycles. In addition, it is recommended to include measures of relevant pharmacodynamic variables to, as early as possible, determine the pharmacokinetic (e.g. AUC) - toxicity/efficacy relationship. This knowledge is useful guidance for the dose selection in later phases in the clinical trial program and is also important in the assessment of the clinical consequences of pharmacokinetic differences in sub-populations. For selected agents the dosing of individual patients can be defined using the maximum tolerated systemic exposure (MTSE) system[1]. If higher exposure is needed in children compared to the therapeutic exposure in adults, the pharmacokinetics in children has to be evaluated with respect to possible non-linearities and the safety margins to preclinical study exposures should be recalculated and evaluated. It is recommended that pharmacokinetic data should be obtained from children of various ages and in particular the peak ages of incidence of the target disease.

[1] Evans WE, Rodman JH, Relling MV, Crom WR, Rivera GK, Pratt CB, Crist WM.. (1991). "Concept of maximum tolerated systemic exposure and its application to phase I-II studies of anticancer drugs". Med Pediatr Oncol **19**(3):153-9.

Appendix 1. Lansky-Play Scale conversion to Karnofsky or WHO Performance Status

For children aged 1 to 12 years old, use of the Lansky play-performance scale is recommended[2].

Lansky Play Performance Scale		Karnofsky Performance Status		WHO Performance Status	
100	Fully active, normal.	100	Normal, no complaints; no evidence of disease.	0	Fully active, able to carry on all pre-disease performance without restriction.
90	Minor restrictions in physically strenuous activity.	90	Able to carry on normal activity; minor signs or symptoms of disease.		
80	Active, but tires more quickly.	80	Normal activity with effort, some signs or symptoms of disease.	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.
70	Both greater restriction of, and less time spent in, active play.	70	Cares for self but unable to carry on normal activity or to do work.		
60	Up and around, but minimal active play; keeps busy with quieter activities.	60	Requires occasional assistance but is able to care for most of personal needs.	2	Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.	50	Requires frequent assistance and medical care.		
40	Mostly in bed; participates in quiet activities.	40	Disabled; requires special care and assistance.	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	In bed; needs assistance even for quiet play.	30	Severely disabled; hospitalisation is indicated although death not imminent.		
20	Often sleeping; play entirely limited to very passive activities.	20	Very ill; hospitalisation and active supportive care necessary.	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	No play; does not get out of bed. Moribund.	10	Moribund, fatal processes progressing rapidly.		
0	Unresponsive. Dead.	0	Unresponsive. Dead.	5	Dead.

[2] Lansky, S. B., M. A. List, et al. (1987). "The measurement of performance in childhood cancer patients." Cancer **60**(7): 1651-6.