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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME

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This guideline replaces Point to Consider on Clinical Investigation of Medicinal Products in the Treatment of Patients with Acute Respiratory Distress Syndrome (CPMP/EWP/504/97)

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GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME

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EXECUTIVE SUMMARY

This Guideline is intended to provide guidance for the evaluation of new medicinal products for prevention and treatment of Acute Respiratory Distress syndrome (ARDS). This Guideline should be read in conjunction with Directive 2001/83/EC as amended, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- Note for Guidance on Clinical Safety Data Management ICH E2
- Note for Guidance on Dose Response Information to Support Drug Registration ICH E4
- Note for Guidance on Good Clinical Practice ICH E6
- Note for Guidance on Studies in Support of Special Populations: Geriatrics ICH E7
- Note for Guidance on General Considerations for Clinical Trials ICH E8
- Note for Guidance on Statistical Principles for Clinical Trials ICH E9
- Note for Guidance on Choice of Control Group in Clinical Trials ICH E10
- Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population ICH E11
- Note for Guidance on the Investigation of Drug Interactions CPMP/EWP/560/95
- Points to Consider on Clinical Investigation of Medicinal Products for the Treatment of Sepsis (in preparation).

This Guideline document is intended to assist applicants during the development of medicinal products for the treatment of ARDS. Alternative approaches may be taken, provided that these are appropriately justified.

The scope of the present document is restricted to drug therapy preventing and treating ARDS. Treatment of underlying clinical conditions will not be considered. In particular the present document does not refer to infectious conditions presenting with a systemic inflammatory response syndrome, e.g. Sepsis, which are addressed in a separate document.

1. INTRODUCTION (background)

Acute Respiratory Distress Syndrome, ARDS, is a catastrophic form of acute lung injury, ALI, with a high mortality rate. ARDS and ALI are distinguished by the degree of hypoxaemia.

A definition of ALI/ARDS was given by the American-European Consensus Conference in 1994 as a syndrome of reduced pulmonary gas exchange caused by diffuse inflammatory processes with increased vascular permeability. The associated clinical, radiological and laboratory abnormalities are not explained by elevations in left atrial or pulmonary capillary pressure. The disease is to be confirmed by the combination of following diagnostic criteria:

- an initiating clinical condition (e.g. sepsis, burns)
- acute onset
- bilateral infiltrates documented by chest radiograph at end-inspiratory position
- pulmonary artery wedge pressure ≤ 18 mmHg and/or absence of clinical evidence of left atrial hypertension
- ALI: PaO_2/FiO_2 ratio ≤ 300 in a stable state after the patient has adapted to standardised ventilation

- ARDS: PaO_2/FiO_2 ratio ≤ 200 in a stable state after the patient has adapted to standardised ventilation.

This definition differentiates ALI from ARDS, so that patients with a ratio of partial pressure of arterial oxygen to a fraction of inspired oxygen of 300 or less are considered to have ALI, whereas those patients with severe hypoxemia and a ratio of 200 or less are considered to have ARDS. However, even if these diagnostic criteria are fulfilled, they allow for the inclusion of a heterogeneous group of patients.

The aetiology of ALI/ARDS is based on different underlying pathophysiological mechanisms. Direct (e.g. concomitant existing pneumonia, aspiration of gastric content, inhalation injury, near drowning) and indirect (e.g. concomitant existing sepsis, multiple trauma, multiple blood transfusion, burns, acute pancreatitis, drug overdose) conditions associated with ARDS have to be distinguished. The most frequent cause is sepsis, accounting for approximately 40% of all cases.

The complex pathophysiology involves an inciting local or systemic event that initiates pulmonary endothelial and epithelial damage and subsequently increased pulmonary permeability. Tachypnoea, hypoxia and respiratory alkalosis are typical early clinical manifestations of ALI that may be followed by the occurrence of diffuse pulmonary infiltrates and respiratory failure within 24 to 48 hours. Early identification and treatment of the underlying condition in combination with aggressive supportive care are essential.

Estimates of the annual incidence of ALI/ARDS vary, but are in the region of 1.5-34 per 100,000 populations per year.

In spite of progress in the intensive care medicine the fatality rate remains high, approximating 40% in ARDS patients. About 90% of deaths occur within the first 2-3 weeks. Irreversible respiratory failure is the cause of death in less than 10% of ARDS patients. After the first three days of ARDS, most deaths are a consequence of multiple organ system failure and/or sepsis. The risk of death is higher for patients with chronic liver disease, non pulmonary organ dysfunction, sepsis and advanced age.

The range of complications of ALI/ARDS is very broad. Frequently occurring complications include baro- and volutrauma, pulmonary hypertension, pneumothorax and bacterial infections.

Abnormal organ function in addition to lung failure caused by ALI/ARDS can develop and may involve the liver, kidney, brain, blood or immune system. These organ dysfunctions may be related to the underlying illness, to treatment or may occur through the same inflammatory process which injured the lungs.

Most patients who survive ARDS have a remarkable degree of recovery of lung function within the first three to six months, given the severity of the initial lung injury. A few patients experience a permanent decrease in lung function.

Pre-existing conditions that predispose to ALI/ARDS include chronic lung disease, chronic alcohol consumption, and advanced age, although ALI/ARDS may occur at any age. Gender seems to play no role.

Currently no approved pharmacological therapy for ARDS is available. ARDS patients are treated with intensive support, which includes various strategies for assisted ventilation. There is some evidence that mechanical ventilation with lower tidal volume maintaining a plateau pressure as low as possible and a sufficient positive end expiratory pressure (PEEP) significantly reduces mortality. High frequency ventilation, inverse ratio ventilation and the prone position are techniques that may shortly improve gas exchange. A large number of treatments have failed to improve survival. These include glucocorticosteroids, surfactant, prostaglandin E_1, ketoconazole, prostacyclin, nitric oxide, and almitrine.

Products for treatment of ARDS can be administered either locally (aerosolization, direct bolus through bronchoscopic instillation [lavage], or via catheter through the endotracheal tube), or systemically (e.g. intravenous).

Standards of and approaches to critical care (e.g. drugs, care, ventilation) in ALI/ARDS may vary between individual physicians, referral centers, and geographical regions. Because many aspects of management of critically ill patients lack a robust evidence base (due to the difficulties in studying this

heterogeneous group of patients as mentioned above), differences in patient management also based on personal opinion and regional custom are common. This all adds to the high degree of heterogeneity within the ALI/ARDS population.

In summary, following important aspects should be attended: high rate of mortality, relative low rate of disability in survivors, heterogeneity of trial populations, need for controlled data, trend for increasing survival with improved ventilator technique, failure of existing medicinal therapy to influence outcome, confounding influences of co-morbid conditions and multi-organ failure. In order to address these difficulties a high degree of standardisation must play a major role in future study design. Planning, coordination, implementation and assessment of such clinical trials present an enormous challenge.

2. PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS

2.1 INCLUSION CRITERIA

Patients recruited for clinical studies for investigation of new therapeutic products for prevention and treatment of ARDS should fulfil the above described diagnostic criteria. In clinical studies for prevention of ARDS the patients should be either already on or candidates for mechanical ventilation (i.e. spontaneous ventilation under positive end-expiratory pressure).

In clinical studies for treatment of ARDS the patients should be mechanically ventilated.

All patients with ALI/ARDS can be included in pivotal trials. A differentiation resulting in stratification between direct and indirect clinical conditions should be presented.

Restricting the inclusion of patients with one, or a limited number of the most common causes of ALI/ARDS (sepsis, aspiration, burn injury etc.) may reduce the degree of heterogeneity but may impact the generalization of results for the indication “prevention and/or treatment of ARDS”. In this case, the indication should reflect the trial population.

2.2 PROGNOSTIC FACTORS AT BASELINE

The following prognostic factors should be reported at baseline and considered in the design and analysis:

- Underlying aetiology of ARDS

  ALI/ARDS is a highly heterogeneous syndrome with aetiologies based on different direct and/or indirect insults as described above. This multifaceted aetiology of ALI/ARDS may have an important influence on outcome. The mortality in the indirect group may be higher than in the direct group due to the involvement of more organs. In addition, it cannot be anticipated that patients with ALI/ARDS of different aetiologies would respond to the same therapy to a similar extent. Therefore, stratified randomisation and analysis should be foreseen for patients with direct and indirect clinical conditions associated with an acute lung injury.

- Function assessment indices

  The severity of ALI/ARDS can be scored according to the modified Murray lung injury score using several easily measured clinical variables: chest radiograph, hypoxemia, positive end-expiratory pressure and lung compliance (based on body height and not on body weight). In addition, further validated both descriptive and prognostic scores, e.g. SOFA (Sequential Organ Failure Assessment); MODS (Multiple Organ Dysfunction Syndrome); APACHE (Acute physiology and Chronic Health Evaluation); SAPS (Simplified Acute Physiology Score), should be documented to describe the severity of the disease and the estimated prognosis.

As these co-variables have an important effect on outcome stratified randomisation should be considered, especially in small or medium size studies. Significant baseline differences between treatment groups for important prognostic factors could make interpretation of the data difficult or impossible.

2.3 CONCOMITANT THERAPY AND CARE

To reduce the degree of heterogeneity confirmatory trials should be planned and conducted with standardised best practice concomitant treatment and care. A minimum standardisation for the following aspects should be discussed in the study protocol and an implementation should be considered as far as possible:

- basic fluid management
- concomitant drug therapy (e.g. muscle relaxation, sedation, stress ulcer prophylactic treatment, prevention of nosocomial infections, prevention of aggregation of thrombocytes)
- artificial nutrition
- timing of concomitant medication
- body positioning
- application of glucocorticosteriods
- mechanical ventilation
- invasive monitoring (especially PAWP).

These measures should be carefully recorded and documented.

It is anticipated that concomitant treatment will be performed according to best standard of care relevant to the European Union. Preferably centres with experience in ARDS therapy and specifically trained investigators should be participating.

3. METHOD TO ASSESS EFFICACY

3.1 PRIMARY ENDPOINTS IN CONFIRMATORY TRIALS

All cause mortality at day 28 since randomisation is the most relevant primary endpoint in confirmatory clinical trials for investigation of new medicinal products in the treatment and prevention of ARDS. In prevention trials the rate of a completely developed picture of ARDS (i.e. all signs of ALI and PaO_2/FiO_2 ratio $\leq$ 200 in a stable state after the patient has adapted to standardised ventilation) might also be acceptable, however, in this case it is recommended to seek regulatory advice.

“Days alive and off ventilator at 28 days after study entry” is no longer recommended as primary endpoint for two reasons:

- Most clinical trials in this indication are open label studies and the decision to wean mechanical ventilation is often subjective.
- This primary endpoint would include days alive and off ventilator between two periods of ventilation (e.g. second phase of mechanical ventilation was necessary due to exhaustion of patient), however these days alive and off ventilator can not be regarded as real clinical benefit.

3.2 SECONDARY ENDPOINTS IN CONFIRMATORY TRIALS

<u>Short Term Secondary Endpoints</u>

Following short-term secondary endpoints should be evaluated: Days alive and off ventilator, days on ICU, days on vaso-active drugs and frequency of complications such as neck/thoracic, gastrointestinal, cardiac, haemodynamic, vascular or barotrauma. These endpoints should be analysed at day 28 since randomisation.

Other short-term secondary endpoints like changes in PaO_2/FiO_2 ratio and other relevant lung parameters during mechanical ventilation and time to the development/resolution of clinically significant organ dysfunction such as renal, hepatic, haematologic, cardiovascular, should also be assessed.

Long Term Secondary Endpoints

All cause mortality rate at six months should be measured. Quality of life may be assessed by using validated cores, e.g. the SF-36 questionnaire in long-term trials. Data with regard to respiratory and neurological function six months after randomisation should be provided.

Follow-up information on these parameters at twelve months should be provided, if necessary as a post licensing commitment.

A treatment that reduces mortality may reduce morbidity, but equally, it may have no effect or even increase morbidity. Therefore, for assessment of the net effect of a therapy a proven benefit in the primary endpoint should also be reflected in the secondary endpoints.

3.3 EFFICACY ENDPOINTS IN EXLORATORY TRIALS

In exploratory trials the impact of heterogeneity on the patient population is complex due to the variety of basic diseases resulting in ARDS and the different concomitant therapy and care. Difficulties in identifying the appropriate setting for an experimental treatment are predictable. It may therefore be advisable to restrict phase II investigations to defined conditions frequently resulting in ARDS, such as sepsis. The choice of primary and secondary endpoints in exploratory trials should be sufficiently justified.

Findings from pharmacodynamic phase II clinical trials should allow integration with findings from confirmatory clinical trials. This may help assessing consistency of results.

In critical care patients with acute lung injury, pharmacokinetics are often altered not only due to changes in drug metabolism and excretion because of impaired organ function, but also due to extracorporeal circulation of blood (including haemofiltration and haemodialysis) with in many cases unpredictable effects on drug elimination. Therefore, the effect of organ malfunction on pharmacokinetics should be investigated.

4. STRATEGY AND DESIGN OF CLINICAL TRIALS

4.1 EARLY STUDIES

In some cases a conduct of early studies in patients rather than healthy volunteers may be necessary for ethical reasons.

PHARMACODYNAMIC STUDIES

Initial human studies should provide preliminary safety data and an estimation of the dose range to be tested in therapeutic studies. The mechanism of action and resulting relevant pharmacodynamic endpoints should be investigated and discussed.

PHARMACOKINETICS STUDIES

The pharmacokinetics of the product should be described and absorption, bioavailability and elimination characterised. An assessment of the extent of systemic absorption of inhaled drugs and their fate is expected.

DOSE RESPONSE RELATIONSHIP

The dose-related benefit and adverse effects should be characterised in randomised studies. The aim of dose-response studies is to define the most effective dose for confirmatory trials. The design depends upon the pharmacology of the test agent.

4.2 MAIN EFFICACY STUDIES

STUDY DESIGN

Randomised clinical trials are required to demonstrate efficacy. It is recognised that fully robust blinding to treatment allocation may not be possible in all cases because a direct administration of placebo to the lung cannot be generally recommended apart from inhaled medicines. Where treatment blinding is not possible and drug administration is open label, assessments should be blinded wherever possible.

A double-blind, randomised study design should be chosen for all placebo-controlled studies with systemically applied medicines or medicines for inhalation.

STRATEGY OF CLINICAL TRIALS

It is not anticipated that all patients will respond to the same therapy to a similar extent because of the heterogeneous pathophysiological mechanisms leading to ALI/ARDS. This expected variability in the characteristics of the patient population decreases the chance of demonstrating efficacy. Designing an appropriate study to investigate an agent that affects one of the multiple pathways involved in producing acute lung injury represents an enormous challenge.

Therefore the following aspects should be considered:

- Time between diagnosis and subsequent inclusion into the study and application of the study medication should be standardised and recorded.
- For exploratory clinical trials it may be advisable to restrict the clinical conditions associated with ARDS to a defined population.
- In large pivotal studies a heterogeneous patient population should be included unless the indication is restricted. Analyses of predefined subgroups (e.g. pre-existing risk factors, aetiology) should support the main findings of the trial.
- All reasonable measures should be taken to ensure that all aspects of management of these patients are the same in both treatment groups. This is especially important in open label studies or where robust blinding to treatment allocation cannot be guaranteed.
- Studies for clinical investigation of medicinal products in patients with acute lung injury are usually multi-centre. To reduce the variability between the individual centres background therapy should be standardised wherever possible. A careful previous investigation of each centre with respect to the recruitment capacity is required and should be documented. Preference should be given to experienced centres with specifically trained investigators and a high recruitment capacity. Randomisation should be stratified by centre. The clinical management of ALI/ARDS should be pre-specified in the protocol and in accordance with European best practice.

CHOICE OF COMPARATOR

At present there is no approved pharmacological treatment that could be considered as an active comparator for trials of ALI/ARDS. The only presently available treatment for ARDS patients is intensified supportive care. Therefore, the current approach to ARDS trial design should be to show superiority of the investigated study drug to best method of care. The supportive regimen should be carefully described in the study protocol.

As long as there is no pharmacological therapy according to current agreed standards in medicine available and approved and as long as the study drug will be used as additive treatment, it is most appropriate to use placebo as a comparator where possible.

Historical data are not acceptable for comparison because of the heterogeneity of trial populations, the variability in causes and co-existing conditions, and the change in mortality that is probably attributable to improvements in mechanical ventilator technique.

4.3 STUDIES IN SPECIAL POPULATIONS

ELDERLY

ALI/ARDS is more common in patients over 65 years of age than in a younger patient population with similar risk factors. Also mortality is higher in critically ill elderly patients. Even if it is not necessary to conduct separate trials in elderly any dossier should provide adequate evidence of risk/benefit in patients over the age of 65.

CHILDREN

ALI/ARDS occurs in all classes of age. Separate trials conducted by paediatric experts and ICU paediatricians, will be needed for children and adolescents, as data from adults cannot readily be extrapolated. As experience is limited regulatory scientific advice is recommended.

NEONATES

Clinical studies for investigation of new medicinal products for prevention and/or treatment of respiratory distress syndrome (RDS) in neonates are a special situation. There are several important differences between RDS and ARDS (e.g. cause of the syndrome, type and number of pre-existing organ failure, impaired and altered metabolism of drugs) in spite of the close histopathological relationship. A detailed recommendation for design, primary and secondary endpoints, stratification for gestational age and concomitant treatment is beyond the scope of the present guideline. Therefore companies should seek scientific advice for their development plan in neonates.

5. CLINICAL SAFETY EVALUATION

5.1 MONITORING OF ADVERSE EVENTS

All adverse events, especially those predicted by the pharmacodynamic properties of the investigational product, should be reported and analysed using a pre-planned methodology. The most important aspects of safety are both short and long term mortality rate.

As for other medicinal products, adverse events need to be fully documented by organ class system.

Any groups at increased risk of adverse events should be identified. Appropriate ways of observing safety for trials in such vulnerable patient populations are warranted. Safety of all patients should generally be surveyed by a Data Monitoring Committee.

Depending on the product, an assessment of antibody formation and/or other immunological parameters might be necessary. Consideration should also be given to the potential interference/contribution of concomitant therapy.

5.2 INTERACTION STUDIES

Critically ill ALI/ARDS patients often have multiple organ function problems, for which they are receiving multiple therapies, resulting in increased probability of interaction all of which may interact with each other. Depending on the mechanism of action and based on the results of non-clinical data and previously conducted clinical trials possible safety concerns arising from PK or PD interactions with commonly co-prescribed medications should be investigated in phase III studies.