化药复方药物临床试验技术指导原则

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1. Background and purpose

Compound drugs refer to drugs containing two or more active ingredients. complex

Prescription drugs should have obvious clinical advantages. The obvious clinical advantages of compound drugs are

The body includes: ÿ Compared with the treatment of one (or more) active ingredients that make up the compound,

Using a combination of drugs can improve the effectiveness, or improve the effectiveness and make it faster

onset of effect. ÿBecause one active ingredient in a compound drug can offset or reduce the effects of another

adverse reactions of an active ingredient, or the dose of the active ingredient in the compound is lower than its individual

standard dosage for drug treatment, thereby improving the safety of compound drugs. ÿWith the group

Compared with the treatment of one (or more) active ingredients in a combination, a combination drug can be

By improving compliance, clinical outcomes can benefit.

This guideline is intended to provide techniques for developing clinical trials of combination drugs.

suggestion. When applying this guidance, reference should also be made to the International Labeling of Pharmaceuticals for Human Use.

The International Council for Harmonization of

Technical Requirements for Pharmaceuticals for Human Useÿ

ICH) and other relevant technical guidelines.

These guidelines represent current recommendations only and will be further developed based on advances in scientific research.

step update. If there are circumstances not covered by this guidance, the regulatory authority should be communicated

comminicate.

2. Scope of application

This guideline mainly focuses on the single drug ingredients in compound drugs with known active ingredients.

Sexual ingredients (active ingredients of marketed drugs with sufficient evidence of safety and effectiveness)

compound drug development. Mainly applicable to chemicals, the general principles also apply

Biological products for therapeutic use. Known for dissociating into two or more species in vivo

Pharmaceutical development of active ingredients may also refer to this guidance. This guideline does not apply to

Used in traditional Chinese medicine compound medicines, and composed of vitamins, trace elements and minerals

of compound drugs.

For the development of compound drugs containing one or more unknown new active ingredients,

Guidelines related to clinical trials of innovative drugs should be followed.

3. Overall consideration of the rationality of the formulation

The single drugs making up the compound drug should have known active ingredients and sufficient clinical

The trial data confirms the effectiveness and safety of each single drug, and each single drug should be the same

The mechanism of action of drugs is widely recognized based on clinical trials and/or clinical practice applications.

OK medicine. Usually, each of the active ingredients that make up a compound drug contributes to the efficacy and/or

Or security has a certain contribution. In some cases, a combination drug

The active ingredient itself has no or very low efficacy for the target indication, but it may

By improving the pharmacokinetic profile of other active ingredients or inhibiting the reduction of drugs

Other factors of efficacy, etc., to improve the efficacy of other active ingredients. For example, contains

Combination drugs of levodopa and carbidopa (carbidopa is a pharmacokinetically enhanced

A compound drug consisting of strong agent), antibacterial drugs and enzyme inhibitors.

The rationality of the compound drug formulation should first be evaluated from the perspective of disease causative factors and

Pathogenesis, mechanism of action of each single drug (for example, the mechanism of action is complementary),

Drug interactions, dosing regimens (e.g., dosing frequency), and coadministration

generalizability (e.g., supporting research literature data and/or references to the combination

Recommendations for combined medication in clinical diagnosis and treatment guidelines) and other aspects will be demonstrated. Should be charged

Analyze the pharmacokinetic/pharmacodynamic characteristics and

Safety and effectiveness, on this basis, fully evaluate the rationality of developing compound drugs

and necessity. If single drug ingredients for different indications are combined into a compound drug

To develop new target indications for drugs, sufficient rationality and necessity basis must be provided.

according to.

Combining active ingredients that treat unrelated diseases into compound medicines is discouraged.

The effectiveness of combination drug therapy relative to the component(s) of the combination should be pre-evaluated.

species) clinical advantages of active ingredient treatments. Its advantages should be through enhanced efficacy or

To demonstrate improved safety, reducing the number of pills taken alone is not enough to prove compound medicines.

obvious clinical advantages.

4. Overall consideration of clinical evidence

Combination drug development should confirm that the combination drug treatment is more effective than the components of the compound.

A clear clinical advantage of treatment with one (or more) active ingredients. compound should be proven

The contribution of each active ingredient in the drug to the efficacy and/or safety, as well as compound drugs

Improve the benefit-risk ratio by enhancing efficacy and/or improving safety.

Clinical evidence that can be provided when applying for marketing includes: clinical trials of compound drugs

Clinical trials that test or combine drugs, or clinical trials combined with literature data. Should be mentioned

Provide adequate pharmacokinetics (PK) and pharmacodynamics

(Pharmacodynamics, PD) and efficacy/safety study data to support

Various dosage strengths of compound drugs are evaluated. If the evidence submitted is joint

Clinical trials of combination drugs also need to pass biological tests on combinations of compound drugs and single drugs.

Efficacy studies prove that combination drugs have similar pharmacokinetics to compound drugs

Characteristics to provide bridging evidence between combination and polypharmacy. Other than biologically equivalent

In addition to sexual research, clinical trials also need to be carried out in accordance with relevant requirements to prove its obvious

Clinical Advantages. For compound drugs consisting of locally administered drugs with local action, then

Guidelines related to clinical trials of locally administered, locally acting drugs should also be followed.

5. Considerations in clinical trial design

The target treatment population positioning of compound drugs usually includes two types: ÿ Loading treatment

Treatment: The therapeutic effect of using any one (or more) active ingredients that make up the compound

Poor patients. ÿ Initial treatment: No single agent in the compound has been used before.

Medication-treated patients.

(1) Loading treatment

1. Pharmacokinetic studies

Human drug interaction studies between active ingredients should generally be conducted except

Not through other evidence (from in vitro experimental data, identification of interaction mechanisms

knowledge or other published clinical trial data) to determine the active ingredients in the compound drug.

There were no pharmacokinetic interactions between doses. If it is determined that combined medication is

If there is no significant impact on clinical safety, drug interactions between active ingredients can be exempted.

Interaction studies.

In some cases, combination drugs may affect the pharmacokinetics of other concomitant drugs.

Potential impact on mechanics and whether to carry out combined use of compound drugs and other drugs

human drug interaction studies, especially if the combination drug contains

Contains pharmacokinetic enhancers (e.g. inhibitors/inducers of metabolic enzymes or transporters

agent).

Special groups (patients with liver and kidney damage, the elderly, etc.) combined medication

Potential drug interactions should also be considered. Available in efficacy/safety studies

Population pharmacokinetic data were used for analysis. If in vitro studies and/or clinical

If clinical data demonstrate no pharmacokinetic interaction, it may be exempted from use in special populations.

Conduct specialized drug interaction studies or population pharmacokinetic analyses.

2. Pharmacodynamics/exploratory trials

Pharmacodynamic data can help understand drug interactions between the active ingredients in a combination drug.

The interaction between efficacy and effect can provide guidance for the dosage selection and proportion composition of compound drugs.

in accordance with.

Factorial design experiments can be used to prove that the relationship between different active ingredients of compound drugs

Are there additive or synergistic effects? When a single active ingredient is present in more than one

When the effective dose level is determined, the factorial design can simultaneously compare different doses of single drugs and different formulations.

Compare the efficacy and safety of the combination with each single drug and placebo. Based on pharmacodynamic indicators

Factorial design studies with endpoints (including all effective dose groups of a single drug) can

Dose finding data are provided. Typically, multiple doses of water should be tested based on a factorial design.

After thorough exploration, select a reasonable ratio and dose based on the test results.

Conduct confirmatory clinical trials on the formulation.

If the combination drug uses a therapeutic dose combination that has been approved for the single drug, it should be provided

Provide sufficient evidence to explain the rationality of the proportion and dose selection of compound drugs.

3. Confirmatory clinical trials

One (or more) active ingredients that make up the compound are required to have poor therapeutic effect

among patients, conduct a randomized controlled clinical trial with superiority design to prove that complex

The prescription has better efficacy than each single drug (or multiple active ingredients) treatment.

For example, patients whose A monotherapy is ineffective can be randomized to receive the AB compound drug.

(or A+B combination), A monotherapy + placebo. Generally speaking, a single drug

Ineffective treatment refers to receiving the optimal dose of treatment and continuing it for a long enough time.

Patients who still have poor efficacy after treatment. If there is clinical justification,

AB combination drugs can also be compared with only A or only with B, but AB combination drugs

The applicable population is limited to A or only patients with poor treatment effect in B. for three

For a compound drug consisting of three active ingredients, it is recommended to prove that the compound contains two of the active ingredients.

Compounds or combinations of ingredients have better efficacy.

In some therapeutic areas, it may be necessary to combine medications with existing standard treatments

comparison, or is preferable to do so. For example, the standard therapy medicine is usually combined with

The individual ingredients in a combination belong to the same therapeutic category and have similar effects,

And it should be demonstrated based on relevant clinical trial evidence, clinical guidelines, etc.

If the target indication population has a chronic disease and requires long-term medication, a link should be provided.

Long-term safety data of combination drugs or compound drugs to support marketing applications,

The application materials should provide true and reliable data that can be used for evaluation.

For other considerations in trial design, such as efficacy endpoints and study duration,

Relevant guidance should be consulted.

(2) Initial treatment

1. Pharmacokinetic studies, pharmacodynamics/exploratory trials

See the corresponding content under "(1) Loading Treatment".

2. Confirmatory clinical trials

Initial treatment refers to giving the patient a combination of drugs immediately for treatment, rather than Another active ingredient is added gradually and individually based on the therapeutic effect. should be pre-assessed and Determine appropriate target populations for initial treatment.

The specific trial design depends on the topic and treatment goals of the compound. It is necessary to prove that the compound A prescription can obtain Better efficacy or safety.

If the target indication population has a chronic disease and requires long-term medication, a link should be provided. Long-term safety data of combination drugs or compound drugs to support marketing applications, The application materials should provide true and reliable data that can be used for evaluation.

The following are considerations regarding formulating compound drugs based on different principles:

(1) Improve effectiveness

1) Each active ingredient in the compound has curative effect

Randomized controlled clinical trials are usually required to demonstrate that combination drugs are effective in Superiority of clinical outcomes at set time points with acceptable safety profile by. Usually a parallel group design can be used, for example, AB compound drug (or A+B Combination drug) A three-arm randomized, parallel controlled trial design comparing single drugs A and B. A full factorial design can be used to provide more data support.

In some cases (e.g. hypertension), combination therapy may be used as initial treatment To improve the efficacy and achieve the expected therapeutic effect faster, clinical trials are required prove.

2) The compound contains a pharmacokinetic (PK) enhancer

If a PK enhancer with a known active ingredient is to be added to the compound, try

For experimental design, please refer to the requirements of item “1)” above. In this case, if based on

There is a reasonable basis for in vitro, preclinical studies and/or pharmacokinetic and pharmacodynamic data.

According to the data, known active ingredients in the compound can be used in randomized controlled clinical trials.

The product can be used as a positive control to carry out superiority testing without setting up pharmacokinetic enhancement.

Strong dose group.

3) The compound contains active ingredients with no or very low efficacy

If one (or more) of the active ingredients in the combination drug itself has an adverse effect on the target

Indications with no or very low efficacy but sufficient mechanism research data (e.g.

If biomarkers are used) indicate their relationship with other active ingredients that make up the combination

There are synergies. Mechanistic research data (e.g. in vitro data), preclinical research

Research and human pharmacodynamic data may suggest that the combination may enhance efficacy. in this case

In this case, it is usually necessary to prove that it is compared with the single drug component in the compound that has the exact therapeutic effect.

Combination drugs can enhance the effectiveness.

(2) Improve safety

If the therapeutic goal of a combination drug is to improve safety, a randomized trial

According to clinical trials, it is proved that compound drugs do not reduce the efficacy compared with single drug treatment.

with better safety/tolerability. If it constitutes a combination drug

If the dose of an active ingredient is lower than its standard monotherapy dose, the combination drug should be

The efficacy and safety of the drug were compared with standard doses of monotherapy. If repeated

One of the active ingredients in the formula can counteract or improve certain effects caused by other active ingredients.

adverse reactions, the primary endpoint of the randomized controlled clinical trial should be specified in advance

Defined adverse reactions, and also need to demonstrate the comparison of combination drugs with monotherapy

The efficacy is not reduced.

If in vitro experimental data, preclinical data and/or human pharmacodynamic data

Demonstrate that the active ingredient that improves safety does not or only contributes little to the target indication.

It has very low efficacy and does not require this active ingredient in randomized controlled clinical trials.

Group.

(3) Situations where single drug treatment is inappropriate or unethical

In areas such as HIV or certain anti-infective treatments, monotherapy is not effective

may lead to the rapid development of drug resistance, so it is appropriate to set monotherapy as the control group

Inappropriate or unethical. In this case, confirmatory clinical trials should

Compare new combination drugs to existing combination drugs or standard combination therapies

Comparison, demonstrating that a new combination drug is comparable to an existing combination drug or standard combination therapy

than, has better efficacy/safety or similar efficacy/safety (non-inferior

effect). New combination medicines may contain similar or different amounts of active

Sexual component.

主要参考文献

1. European Medicines Agency, Committee for Medicinal Products for Human use (CHMP). Guideline on clinical development of fixed combination medicinal products. 1 October 2017.

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3. FDAÿHypertension: Developing Fixed-Combination Drug Products for Treatment Guidance for Industryÿ2018ÿ.