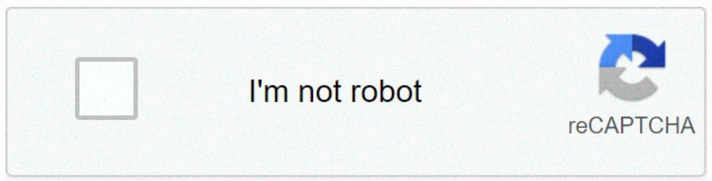

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Investigator brochure medical device template

7.1 Introduction The investigator's Brochure (IB) is a set of clinical and non-clinical data on the investigational medicinal product(s) relevant for the study of the medicinal product(s) in humans. Its purpose is to provide investigators and other trial participants with information that will facilitate their understanding of the reasons and their adherence to many key elements of the protocol, such as dose, frequency/interval of doses, routes of administration: and safety monitoring procedures. IB also provides an overview to support the clinical management of study participants during the clinical trial. The information should be presented in a concise, simple, objective, balanced and non-promotional form that allows the doctor or potential investigator to understand them and carry out his own impartial risk-benefit assessment of the appropriateness of the proposed trial. Therefore, a person with medical qualifications should generally participate in adaptation IB, but the content of IB should be approved by the disciplines that produced the data described above. This Guideline shall define the minimum information to be included in IB and provide proposals for its organisation. It is expected that the type and extent of information available will vary depending on the stage of development of the product under investigation. If the investigational medicinal product is placed on the market and is generally understood by doctors in its pharmacology, extensive IB may not be necessary. If the regulatory authorities so permit, a brochure with basic product information, package leaflet or labelling may be a suitable alternative, provided that it contains current, comprehensive and detailed information on all aspects of the examiner's product that might be relevant to the examiner. If a product placed on the market is being investigated for new uses (i.e. a new indication), an IB specific to this new use should be prepared. IB should be reviewed at least once a year and revised as necessary in accordance with the adjuthrator's written procedures. Depending on the stage of development and the production of relevant new information, a more frequent revision may be more appropriate. However, in accordance with good clinical practice, the relevant new information may be so important that it is communicated to the investigators and, where applicable, to the Institutional Review Committees (IEC)/Independent Ethics Committee (IEC) and/or regulatory authorities before it is included in the revised IB. The sponsor is generally responsible for ensuring that up-to-date IB is available to researchers and that investigators are responsible for providing up-to-date IB. In the case of a trial sponsored by a researcher, the sponsor-researcher should determine whether the brochure is available from a commercial manufacturer. If the test product is provided by the investigator-examiner, then the provide the necessary information to the test staff. In cases where the preparation of a formal IB is impractical, the investigator-examiner should provide as a substitute an extended section of background information in the test report containing at least the up-to-date information described in this Guideline. 7.2 IB's general considerations should include: 7.2.1 The name of the Site This should provide the name of the sponsor, the identity of each product under investigation (i.e. research number, chemical or approved generic name and trade name(s), if legally permissible and requested by the sponsor) and the date of issue. It is also proposed to provide an issue number and a reference to the number and date of issue it replaces. An example is given in Appendix 1. 7.2.2 Confidentiality Statement The sponsor may wish to include a statement ordering the examine/consignee to treat IB as a confidential document for exclusive information and use of the investigation team and the IRB/IEC. 7.3 The content of the IB investigative brochure should contain the following sections, each with literature references, if applicable: 7.3.1 Content The content example is given in Appendix 2 7.3.2 Summary A concise summary (preferably not exceeding two pages) should be provided highlighting the relevant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic and clinical information relevant to the clinical development stage of the investigational medicinal product. 7.3.3 Introduction A brief introductory statement should be provided containing the chemical name (and the common and trade name(s) if all active substances are approved, the pharmacological substance(s) of the investigational medicinal product(s) and its expected position in this class (e.g. benefits), the rationale for carrying out research on the products under investigation and the presumed prophylactic, therapeutic or diagnostic indication(s). Finally, the introductory statement should provide a general approach to be followed when assessing the product under investigation. 7.3.4 The physical, chemical and pharmaceutical properties and formula A should provide a description of the substances of the product under investigation (including the chemical and/or structural formula(s)) and a brief summary of the relevant physical, chemical and pharmaceutical properties should be provided. In order to allow for appropriate precautions to be taken during the experiment, a description of the formulation(s) to be used, including excipients, should be provided and justified where clinically relevant. Instructions for storing and handling dosing forms should also be provided. Any structural similarities with other known compounds should be reported. 7.3.5 Preclinical studies Introduction: Results of all relevant non-clinical pharmacological, toxicological, pharmacokinetic and investigational products studies should be provided in an aggregated form. This summary should address the methodology used, the results and the discussion of the relevance of the findings for the therapeutic and potential adverse and unintended effects on humans investigated. The information provided may include, where appropriate: - Nature and frequency of pharmacological or toxic effects - Severity or intensity of pharmacological or toxic effects - Time to onset of effects - Reversibility of effects - Duration of effects - Dose response Test species Number and sex of animals in each group Unit dose (e.g. Milligram/kilogram (mg/kg)) Dosing interval Dosing route Duration of dosing Duration Of systemic distribution Duration of subsequent results after exposure Including the following aspects: Tabular format/lists should be used whenever possible to improve presentation clarity. The following sections should discuss the most important findings from studies, including the response of observed dose effects, relevance to humans and all aspects to be studied in humans. Where appropriate, effective and non-toxic dose findings in the same species should be compared (i.e. the therapeutic index should be discussed). The relevance of this information to the proposed human behavior should be addressed. Where possible, blood/tissue levels should be compared rather than mg/kg. (a) Preclinical pharmacology A summary of the pharmacological aspects of the products under investigation and, where appropriate, of its major metabolites studied in animals should be included. Such a summary should include studies assessing potential therapeutic activity (e.g. efficacy models, receptor binding and specificity) as well as safety assessment studies (e.g. specific studies to assess pharmacological measures other than the intended therapeutic effects). (b) Pharmacokinetics and metabolism of products in animals A summary of the pharmacokinetics and biological transformation and disposition of investigational medicinal products in all species studied should be provided. The discussion of the findings should address the absorption and local and systemic bioavailability of the products and metabolites studied and their relationship to pharmacological and toxicological findings in animal species. (c) Toxicology Summary of toxicological effects surveyed in relevant studies conducted in different species should be described, where appropriate, in the following headings: 7.3.6 Effects on humans Introduction: A thorough discussion should be provided on the known effects of investigational medicinal products in humans, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided on the any use of test products other than clinical trials, such as experience during marketing. (a) Pharmacokinetics and metabolism of products in humans. (b) Safety and efficacy Summary of safety information of the investigational medicinal product(s) (including metabolites, where appropriate) safety, pharmacodynamics, efficacy and dose response obtained from previous human studies (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where several clinical trials have been completed, the use of safety and efficacy summaries in several trials as indicated in subgroups may provide a clear presentation of the data. Tabulation summaries of adverse drug reactions would be useful for all clinical studies (including those for all indications studied). Important differences in models/incidences of adverse drug reactions between indications or subgroups should be discussed. IB should provide a description of the potential risks and adverse reactions to the medicinal product to be expected from previous experience with the medicinal product under investigation and the related medicinal product. A description of the preventive measures or specific monitoring to be carried out as part of the examination of the use of the product(s) should also be provided. (c) Experience with the placing on the market of bib should identify the countries in which the product under investigation has been placed on the market or approved. All relevant information resulting from the use of the product after placing it on the market (e.g. formulations, doses, routes of administration and adverse drug reactions) should be summarised. IB should also identify all countries where the product under investigation has not received a marketing authorisation/registration or has been withdrawn from placing on the market/registration. 7.3.7 Summary of data and guidelines for the investigator This section should provide an overall debate on preclinical and clinical data and summarise information from different sources on the different aspects of the products tested where possible. In this way, investigators may be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, published reports on related products should be discussed. This could help the investigator anticipate adverse drug reactions or other problems in clinical trials. The overall objective of this section is to provide investigators with a clear understanding of the potential risks and adverse reactions and specific tests, observations and precautions that may be necessary for the clinical trial. This understanding should be based on available physical, chemical, pharmaceutical, pharmacological, toxicological and clinical information on the product(s) being tested. The clinical trial should also be provided with guidance on the recognition and treatment of adverse drug reactions based on previous human experience and the pharmacology of the product under investigation 7.4 APPENDIX 1: TITLE PAGE (Example) SPONSOR NAME Product: Research Number: Name(s): Chemical, General (if approved) Business name (if legally admissible and required by sponsor) Investigator's issue number: Date of issue: Replaces previous issue number: Date: 7.5 APPENDIX 2: CONTENTS OF THE INVESTIGATOR'S BROCHURE (Example) - Confidentiality statement (optional) ..... 1 Content ..... 2 Summary ..... 3 Introduction ..... 4 Physical, chemical and pharmaceutical properties and formulation ..... 5 Preclinical study ..... 5.1 Preclinical pharmacology ..... 5.2 Pharmacokinetics and metabolism of products in animals ..... 5.3 Toxicology ..... 6 Effects in humans ..... 6.1 Pharmacokinetics and metabolism of products in humans ..... 6.2 Safety and efficacy ..... 6.3 Marketing experience ..... 7 Summary of data and guidelines for the investigator ..... NB: References to 1. Publications 2. Messages These references should be found at the end of each chapter Supplements (if any) Single dose carcinogenicity In special studies (e.g. Irritability and sensitisation) Reproductive toxicity Genotoxicity (mutagenicity) A summary of information on the pharmacokinetics of the investigational medicinal product(s) should be submitted, including, where available: pharmacokinetics (including metabolism, where appropriate, and absorption, plasma protein binding, distribution and elimination). Bioavailability of the products under investigation (absolute, if possible and/or relative) using the reference dosing formulation. Population subgroups (e.g. gender, age and impaired organ function). Interactions (e.g. interactions and effects of food). Other pharmacokinetic data (e.g. results of population studies conducted in clinical trials). Introduction The investigator's Brochure (IB) is a compilation of clinical and non-clinical data on the investigational medicinal product(s) relevant for the study of the medicinal product(s) in humans. Its purpose is to provide investigators and other trial participants with information that will facilitate their understanding of the reasons and their adherence to many key elements of the protocol, such as dose, frequency/interval of doses, routes of administration: and safety monitoring procedures. IB also provides an overview to support the clinical management of study participants during the clinical trial. The information should be presented in a concise, simple, objective, balanced and non-promotional form that allows the doctor or potential investigator to understand them and carry out his own impartial risk-benefit assessment of the appropriateness of the proposed trial. Therefore, a person with medical qualifications should generally participate in adaptation IB, but the content of IB should be approved by the disciplines that produced the data described above. This Guideline shall define the minimum information to be included in IB and provide proposals for its organisation. It is expected that the type and extent of information available will vary depending on the stage of development of the product under investigation. If the investigational medicinal product is placed on the market and is generally understood by doctors in its pharmacology, extensive IB may not be necessary. If the regulatory authorities so permit, a brochure with basic product information, package leaflet or labelling may be a suitable alternative, provided that it contains current, comprehensive and detailed information on all aspects of the examiner's product that might be relevant to the examiner. If a product placed on the market is being investigated for new uses (i.e. a new indication), an IB specific to this new use should be prepared. IB should be reviewed at least once a year and revised as necessary in accordance with the adjuthrator's written procedures. Depending on the stage of development and the production of relevant new information, a more frequent revision may be more appropriate. However, in accordance with good clinical practice, the relevant new information may be so important that it is communicated to the investigators and, where applicable, to the Institutional Review Committees (IEC)/Independent Ethics Committee (IEC) and/or regulatory authorities before it is included in the revised IB. The sponsor is generally responsible for ensuring that up-to-date IB is available to researchers and that investigators are responsible for providing up-to-date IB. In the case of a trial sponsored by a research trial, the sponsor-examiner should determine whether the available from a commercial manufacturer. If the test product is provided by a sponsor-researcher, then it should provide the necessary information to the test staff. In cases where the preparation of a formal IB is impractical, the investigator-examiner should provide as a substitute an extended section of background information in the test report containing at least the up-to-date information described in this Guideline. 7.2 IB's general considerations should include: 7.2.1 The name of the Site This should provide the name of the sponsor, the identity of each product under investigation (i.e. research number, chemical or approved generic name and trade name(s), if legally permissible and requested by the sponsor) and the date of issue. It is also proposed to provide an issue number and a reference to the number and date of issue it replaces. An example is given in Appendix 1. 7.2.2 Confidentiality Statement The sponsor may wish to include a statement ordering the examine/consignee to treat IB as a confidential document for exclusive information and use of the investigation team and the IRB/IEC. 7.3 The content of the IB investigative brochure should contain the following sections, each with literature references, if applicable: 7.3.1 Content The content example is given in Appendix 2 7.3.2 Summary A concise summary (preferably not exceeding two pages) should be provided highlighting the relevant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic and clinical information relevant to the clinical development stage of the investigational medicinal product. 7.3.3 Introduction A brief introductory statement should be provided containing the chemical name (and the common and trade name(s) if all active substances are approved, the pharmacological substance(s) of the investigational medicinal product(s) and its expected position in this class (e.g. benefits), the rationale for carrying out research on the products under investigation and the presumed prophylactic, therapeutic or diagnostic indication(s). Finally, the introductory statement should provide a general approach to be followed when assessing the product under investigation. 7.3.4 The physical, chemical and pharmaceutical properties and formula A should provide a description of the substances of the product under investigation (including the chemical and/or structural formula(s)) and a brief summary of the relevant physical, chemical and pharmaceutical properties should be provided. In order to allow for appropriate precautions to be taken during the experiment, a description of the formulation(s) to be used, including excipients, should be provided and justified where clinically relevant. Instructions for storing and handling dosing forms should also be provided. Any structural similarities with other known compounds should be reported. 7.3.5 Study Introduction: The results of all relevant studies of inclinical pharmacology, toxicology, pharmacokinetics and metabolism of the products studied should be provided in an aggregated form. This summary should address the methodology used, the results and the discussion of the relevance of the findings for the therapeutic and potential adverse and unintended effects on humans investigated. The information provided may include, where appropriate: - Nature and frequency of pharmacological or toxic effects - Severity or intensity of pharmacological or toxic effects - Time to onset of effects - Reversibility of effects - Duration of effects - Dose response Test species Number and sex of animals in each group Unit dose (e.g. Milligram/kilogram (mg/kg)) Dosing interval Dosing route Duration of dosing Duration Of systemic distribution Duration of subsequent results after exposure Including the following aspects:

Tabular format/lists should be used whenever possible to improve presentation clarity. The following sections should discuss the most important findings from studies, including the response of observed dose effects, relevance to humans and all aspects to be studied in humans. Where appropriate, effective and non-toxic dose findings in the same species should be compared (i.e. the therapeutic index should be discussed). The relevance of this information to the proposed human behavior should be addressed. Where possible, blood/tissue levels should be compared rather than mg/kg. (a) Preclinical pharmacology A summary of the pharmacological aspects of the products under investigation and, where appropriate, of its major metabolites studied in animals should be included. Such a summary should include studies assessing potential therapeutic activity (e.g. efficacy models, receptor binding and specificity) as well as safety assessment studies (e.g. specific studies to assess pharmacological measures other than the intended therapeutic effects). (b) Pharmacokinetics and metabolism of products in animals A summary of the pharmacokinetics and biological transformation and disposition of investigational medicinal products in all species studied should be provided. The discussion of the findings should address the absorption and local and systemic bioavailability of the products and metabolites studied and their relationship to pharmacological and toxicological findings in animal species. (c) Toxicology Summary of toxicological effects found in relevant studies carried out on different species should be described, where appropriate, in the following headings: 7.3.6 Effects in humans Introduction: A thorough discussion should be provided on the known effects of the products tested in humans, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other Activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided concerning the results of any use of the products tested other than in clinical trials, such as experience during marketing. (a) Pharmacokinetics and metabolism of products in humans. (b) Safety and efficacy Summary of safety information of the investigational medicinal product(s) (including metabolites, where appropriate) safety, pharmacodynamics, efficacy and dose response obtained from previous human studies (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where several clinical trials have been completed, the use of safety and efficacy summaries in several trials as indicated in subgroups may provide a clear presentation of the data. Tabulation summaries of adverse drug reactions would be useful for all clinical studies (including those for all indications studied). Important differences in models/incidences of adverse drug reactions between indications or subgroups should be discussed. IB should provide a description of the potential risks and adverse reactions to the medicinal product to be expected from previous experience with the medicinal product under investigation and the related medicinal product. A description of the preventive measures or specific monitoring to be carried out as part of the examination of the use of the product(s) should also be provided. (c) Experience with the placing on the market of bib should identify the countries in which the product under investigation has been placed on the market or approved. All relevant information resulting from the use of the product after placing it on the market (e.g. formulations, doses, routes of administration and adverse drug reactions) should be summarised. IB should also identify all countries where the product under investigation has not received a marketing authorisation/registration or has been withdrawn from placing on the market/registration. 7.3.7 Summary of data and guidelines for the investigator This section should provide an overall debate on preclinical and clinical data and summarise information from different sources on the different aspects of the products tested where possible. In this way, investigators may be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, published reports on related products should be discussed. This could help the investigator anticipate adverse drug reactions or other problems in clinical trials. The overall objective of this section is to provide investigators with a clear understanding of the potential risks and adverse reactions and specific tests, observations and precautions that may be necessary for the clinical trial. This understanding should be based on available physical, chemical, pharmaceutical, pharmacological, toxicological and the products examined. The clinical investigator should also be provided with guidance on the recognition and treatment of possible overdoses and adverse drug reactions based on previous human experience and the pharmacology of the investigational medicinal product 7.4 APPENDIX 1: PAGE TITLE (Example) SPONSOR NAME Product: Research No:Name: Chemical, Generic (if approved) Trade name (if legally permissible and required by sponsor) ISSUE NUMBER OF THE INVESTIGATOR'S BOOKLET : Date of issue: Replaces previous issue Number: Date: 7.5 APPENDIX 2: CONTENTS OF THE INVESTIGATOR'S BROCHURE (Example) - Confidentiality statement (optional) ..... 1 Content ..... 2 Summary ..... 3 Introduction ..... 4 Physical, chemical and pharmaceutical properties and formulation ..... 5 Preclinical study ..... 5.1 Preclinical pharmacology ..... 5.2 Pharmacokinetics and metabolism of products in animals ..... 5.3 Toxicology ..... 6 Effects in humans ..... 6.1 Pharmacokinetics and metabolism of products in humans ..... 6.2 Safety and efficacy ..... 6.3 Marketing experience ..... 7 Summary of data and guidelines for the investigator ..... NB: References to 1. Publications 2. Messages These references should be found at the end of each chapter Supplements (if any) Single dose carcinogenicity In special studies (e.g. Irritability and sensitisation) Reproductive toxicity Genotoxicity (mutagenicity) A summary of information on the pharmacokinetics of the investigational medicinal product(s) should be submitted, including, where available: pharmacokinetics (including metabolism, where appropriate, and absorption, plasma protein binding, distribution and elimination). The bioavailability of the products under investigation (absolute, if and/or relative) using the reference dosing formulation. Population subgroups (e.g. gender, age and impaired organ function). interactions (e.g. drug-product interactions and food effects). Other pharmacokinetic data (e.g. results of population studies conducted in clinical trials). Page 3 7.1 Introduction Investigator information (IB, investigator's brochure) is a set of clinical and preclinical data on the investigational medicinal product(s) relevant to the human clinical trial(s). The purpose of the investigator's information is to make available to researchers and other persons involved in the clinical trial information enabling them to understand and adhere to the essential points of the test plan, such as. B dose, frequency/intervals of dosing, type of application and safety monitoring measures. Investigator information shall provide further information to assist in the medical care of participants during the clinical trial. The information should be presented in a concise, simple, objective, balanced form and without advertising, so that the physician or potential investigator can understand and carry out his or her own impartial risk/benefit assessment as regards the adequacy of the proposed clinical trial. For this reason, the processing of information should normally be carried out by a person with medical qualifications. However, the content of the auditor's information should be approved by the experts who collected the data described above. This Guideline sets out the minimum amount of information that should be included in the auditor's information and has made proposals on their proposal. It should be assumed that the nature and extent of the information available depends on the stage of development of the investigational medicinal products. If the investigational medicinal product is on the market and its pharmacology is well known to the general practitioner, extensive information on the examination may not be required. Where the competent authorities so permit, information on professional use, package leaflet or labelling may be an appropriate alternative, provided that they contain up-to-date, comprehensive and detailed information on all aspects of the investigational medicinal product which may be relevant to the investigator. If the product is to be tested for a new application (i.B. new data), information should be created for the auditor to respond specifically to the new application. The auditor's information should be reviewed at least once a year and, if necessary, revised in accordance with the adjuthration authority's written procedures. Depending on the stage of development and publication of new relevant data, a more frequent revision may be required. New however, they may be so important that, in accordance with the GCP, they are communicated to auditors and, where applicable, to the IRB/independent ethics committees and/or to the competent authority(s) before being included in the revised auditor's information. The sponsor is generally responsible for ensuring that the auditor is provided with up-to-date information on the reviewer. The auditors shall be responsible for forwarding up-to-date information to the auditors to the relevant irb/independent ethics committees. If the investigator is also the sponsor of the clinical trial, it should examine whether information from the investigator is available from the manufacturer. Provided that the investigational medicinal product is provided by a sponsoring investigator, it should provide the necessary information to the personnel involved in the clinical trial. Where the preparation of information on the formal reviewer is not feasible, the sponsor of the review should include in the audit plan, as a substitute, a detailed part with supporting information containing at least the information described in this Guideline in its current form. 7.2 General considerations Auditor's information should include: 7.2.1 The title page Here should be the name of the sponsors, the identification of all the preparations examined (i.e. research number, chemical name or approved generic name, as well as trade name (trade name), if legally permissible and requested by the sponsor) and date of issue. It is also recommended that you provide a version number and a reference to the number and date of the previous version. Example is given in Appendix 1. 7.2.2 Confidentiality It may be in the sponsor's interest to include a statement in which the investigator/recipient is authorised to treat the investigator's information as a confidential document for exclusive information and the use of the information and its use by the investigator and his staff involved in the clinical trial, as well as the IRB/Independent Ethics Committee. 7.3 Content of the information investigator The investigator information should contain the following sections, for which literature references should be provided where appropriate: 7.3.1 Content Annex 2 gives an example of content. 7.3.2 Summary The investigator's information should include a brief summary (preferably not longer than two pages) highlighting the basic known physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic and clinical information relevant to the clinical development stage of the study substance. 7.3.3 Introduction A brief introduction should be provided for the chemical name of the substance under investigation (as well as the generic name(s) and trade name(s), if authorised, of all active substances class of substances as well as its expected position within that class (e.g.B benefits), justification of research activities with the investigator product(s) as well as expected prophylactic, therapeutic or diagnostic indications. The introduction should describe the general approach to be used in the investigation of the investigational medicinal product. 7.3.4 Physical, chemical and pharmaceutical properties and dosage form All components of the product under investigation (including chemical and/ or structural formulae) should be described and the relevant physical, chemical and pharmaceutical properties summarised briefly. In order to take appropriate precautions during a clinical trial, a description of the dosage forms used, including nasal agents, should be provided and, where clinically relevant, justified. Instructions on the storage and handling of dosing forms should also be provided. Any structural similarities with other known chemical compounds should be reported. 7.3.5 Preclinical studies Introduction: The results of all relevant preclinical studies of pharmacology, toxicology, pharmacokinetics and metabolism of investigational medicinal products should be presented in summary form. The summary should set out the methods and results used and discuss the relevance of the observations in relation to the therapeutic and potential adverse and adverse effects on humans to be investigated. The information provided may, where appropriate, cover the following aspects (if known/available): the number of animal species studied and the sex of the animals in each dosing unit of the group (e.B., milligrams / kilogram [mg / kg]) type of dosing interval of application Duration of administration Information on the systemic duration of distribution of subsequent examination after the results, including the following aspects: type and frequency of pharmacological or toxic effects Severity or intensity of pharmacological or toxic effects Time to onset of effects reversibility of effects Duration of effects Dose-response relationship As far as possible, tables/ lists should be used for a clear presentation. The main results of the studies should be discussed in the following sections, including dose dependence on observed effects, relevance to humans and aspects to be studied in humans. Where possible, effective and non-toxic doses derived from the same species should be compared (i.e. the therapeutic index should be discussed). The relevance of this information from the point of view of human Dosing should be addressed. As far as possible, comparisons should not be compared on the basis of [mg/ kg], but on blood/tissue levels. (a) Preclinical pharmacology The pharmacological aspects of the investigational medicinal products and, where appropriate, its essential metabolites identified in animal experiments should be summarised. Studies to evaluate the potential therapeutic efficacy (e.g. B models of efficacy, binding to receptors and specificity) and safety (e.g.B specific studies to evaluate the pharmacological effects occurring together with the intended therapeutic effect(s).b) The pharmacokinetics and metabolism of the preparation in animals The summary of pharmacokinetics and biological conversion and excretion of the investigational medicinal product in all animal species studied should be included. The discussion of the results should include the absorption and local and systemic availability of the test substance and its metabolites and their relationship to pharmacological and toxicological outcomes in animals. (c) Toxicology Summary of toxicological effects detecting in relevant tests on different animal species should be prepared under the following headings, if necessary: Single administration Re-administration of carcinogenicity Specific studies (e.B. Triggering irritation and sensitisation) Reproductive toxicity Genotoxicity (mutagenicity) 7.3.6 Effects in humans Initiation: It should include a comprehensive discussion of the known effects of the investigational medicinal product(s) on humans, including information on pharmacokinetics, metabolism, pharmacodynamics, dose effect, safety, efficacy and other pharmacological effects. Where possible, an overview of all completed clinical trials should be provided. Similarly, information should be provided on the results obtained from the use of the investigational medicinal product outside clinical trials, e.B. experience with the commercial product (a) human pharmacokinetics and metabolism A summary of data on the pharmacokinetics of the investigational medicinal product(s), including pharmacokinetics (including metabolism, where appropriate, and absorption, plasma protein binding, distribution and elimination) should be provided. Bioavailability of the investigational preparation (absolutely, as far as possible, and / or relative) using the reference dose form. Population subgroups (.B gender, age, impaired organ function). interactions (e.g. B interactions with other preparations and foodstuffs). Other pharmacokinetic data (e.g. . B. the results of population studies conducted in one or more clinical trials carried out.) (b) Safety and efficacy A summary of data on safety, pharmacodynamics, efficacy and dose-response relationship of investigational medicinal products (including metabolites, if possible) obtained from previous clinical trials in subjects and/or patients should be provided. The scope of this information should be discussed. If several clinical studies have already been completed, safety and efficacy data may be clear when summarised by indications and subgroups. Tabulated summaries of adverse drug reactions from all clinical trials (including all test indications) would be useful. Important differences in models/ frequencies of adverse reactions between indications or subgroups should be discussed. Investigator information should provide a description of possible risks and adverse reactions to the investigational medicinal product and related medicinal products on the basis of past experience. In addition, the precautions or specific monitoring measures to be taken when using the investigational medicinal product in clinical research should be described. (c) Experience with a commercial medicinal product Investigator's information should include countries where the investigational medicinal product has been placed on the market or authorised. All essential information obtained during use after placing the product on the market (e.g. B dosing forms, doses, types of use and undesirable effects) should be summarised. In addition, the investigator's information should indicate the countries where the investigational medicinal product has not received a marketing authorisation/ marketing authorisation or where it has been withdrawn from the market/ has lost its approval. 7.3.7 Summary of data and guidelines for the investigator In this section, preclinical and clinical data need to be comprehensively discussed and information from different sources summarised as soon as possible on the different aspects of the investigational medicinal product. In this way, investigators may be provided with an optimal interpretation of the available data, together with an assessment of these data and their impact on the clinical trial. Where appropriate, publications on related products should be discussed. This could help the investigator to calculate in advance adverse drug reactions or other problems in clinical trials. The main objective of this section is to provide the investigator with a clear picture of the potential risks and adverse reactions and specific examinations, observations and precautions that may be necessary in a clinical trial. This knowledge should be based on the available chemischen, pharmazeutischen, pharmacologischen, toxicologischen und klinischen Informationen zum / zu den Pr.f.p.det(en) gest.tzt sein. Weiterhin sollte der klinische Pr'fer angeleitet werden, eine m'glyche 'beberdosierung und unerw'nschte Arzneimittelwirkungen zu erkennen und zu behandeln, beruhend auf bisherigen Erfahrungen am Menschen und der Pharmakologie des Pr.p.p.pents zur.ckgegriffen wird. 7.4 ANHANG 1: TITELSEITE (Beispiel) MENO DES SPONZOROV Produkt: Forschungsnummer: Bezeichnungen: Chemisch, generisch (falls registriert) Handelsnamen (falls gesetzlich zul'ssig und vom Sponsor gew'nscht) PR'FERINFORMATION Versionsnummer: Datum der Freigabe: Ersetzt mmer: Údaj: 7,5 ANHANG 2: INHALTSVERZEICHNIS EINER PR-FERINFORMATION (Beispiel) -Vertraulichkeitserkl.rung (wahlweise) -Unterschriftenseite (wahlweise) 1 Inhaltsverzeichnis 2 Zusammenfassung 3 Einleitung 4 Fysikalische, chemische und pharmazeutische Eigenschaften und Darreichungsform 5 Pr'klinische Studien 5.1 Pr'klinische Pharmakologie 5.2 Pharmakokinetik und Metabolismus beim Tier 5.3 Toxikologie 6 Wirkungen am Menschen 6.1 Pharmakokinetik und Metabolismus am Menschen 6.2 Unbedenklichkeit und Wirksamkeit 6.3 Erfahrungen mit dem Handelspr.parat 7 Zusammenfassung der Daten und Anleitung f.r Pr.fer Hinweis: Verweise auf 1. Ver-ffentlichungen 2. Berichte Diese Literaturangaben sollten am Ende jedes Kapitels aufgef-hrt werden. Anh'nge, sofern vorhanden Page 4 7.1 Introduction the Investigator's Guide (MI) contains clinical and non-clinical data relevant for the study of medicinal products in human research. It aims to provide researchers and others involved in the experiment with information enabling them to understand the reason and reason why key aspects of the protocol, such as dosage and interval, and the form of administration and procedures for monitoring safety, need to be followed. IM shall also adequately guide the clinical report of the study participants during the conduct of the clinical trial. The information should be presented in a concise, simple, objective, balanced and non-promotional manner that allows clinicians or potential researchers to carry out a non-scientific risk-benefit assessment and the relevance of the proposed clinical trial. For this reason, the doctor should generally participate in the preparation of im, although its content must be approved by the experts who produced the described data. This guide defines the minimum information that should be included in the MI and contains suggestions on its format. It is expected that the type and extent of information available will vary depending on the development phase of the drug being investigated. If the investigational medicinal product is placed on the market and its pharmacology is widely known to doctors, extensive MI may not be necessary. Where the legislation so permits41, a guide with basic product information, the package leaflet may be a suitable alternative, provided that it is ensured that it contains up-to-date, clear and detailed information on all necessary aspects of the investigational drug which are relevant to the investigator. Where a medicinal product placed on the market is being investigated for a new use (e.g. a new indication), a specific IM should be prepared for that new use. Depending on the stage of development and the relevance of the new information, more frequent examination may be necessary. However, according to the CFP, all new relevant information should be communicated to the relevant investigators and CEIC and regulators before it is included in the updated VS. In the case of an experiment in which the promoter is an examiner, the investigator shall determine whether the holder of the manufacturer has a manual. If the investigational medicinal product is supplied by a promoter-researcher, the promoter should provide the necessary information to the test staff. In cases where the preparation of a formal IC is in practice, the promoter-researcher should, as an alternative, include in the test report an extended part of the background information containing the updated minimum information described in this guide. 7.2 General considerations The Manual for Investigators should contain: 7.2.1 The front page Of the Promoter Name, the identity of each investigation medicinal product (e.g. research number, chemical name or common name and trade name should be given where legally possible and requested by the promoter) and the date of issue. It is also proposed to provide an issue number and a reference to the number and date of issue it replaces. An example is given in Annex 1. 7.2.2 The Promoter's Confidentiality Statement may contain a statement ordering the hearing officer and other recipients to treat the MI as a confidential document solely for the purpose of informing and using investigative equipment and CEIC. 7.3 Contents of the hearing officer's manual. It should contain the following sections, each with bibliographical references, if necessary. 7.3.1 Index An example of the summary of Appendix 2 7.3.2 A brief summary (preferably with a maximum extension to two pages) is given, highlighting the important and available physical, chemical, pharmacological, pharmacological, toxicological, pharmacokinetic, metabolic and clinical information relevant to the clinical development phase subject to investigation. 7.3.3 Introduction A brief introduction containing the chemical name (and common name and trade name, if authorised) of the investigational medicinal product, all active substances, the pharmacological class of the investigational medicinal product and differences from those of its classes (e.g. benefits), the justification for conducting the proposed clinical trial with the medicinal product and its intended prophylactic, therapeutic and diagnostic indications must be given. Finally, the introduction should provide a general approach to be followed when assessing the drug under investigation. 7.3.4 Physical, chemical and pharmacological properties and formula A description of the active substances of the substance under investigation (including the chemical and/or structural formula) should be provided and a concise summary of the relevant physical, chemical and pharmacological properties should be provided. In order to allow appropriate precautions to be taken during the experiment, a description of the formulation used, including excipients, where clinically relevant, should be provided and justified. Instructions for the storage and administration of pharmaceutical forms should also be provided. Any structural similarity to other known compounds should be reported. 7.3.5 Preclinical studies Introduction: The results of all relevant non-clinical studies of pharmacology, toxicology, pharmacokinetics and metabolism of medicinal products in research should be provided in an aggregated form. This summary should consider the methodology used, the results and the discussion of the relevance of the findings for the therapeutic indication investigated and possible adverse and unintended effects on humans. The information provided includes, where appropriate or available: • Species studied • Number and sex of animals in each group • Dosing unit (e. g. milligram/kilogram (mg/kg)• Dose interval • Via administration • Dosing interval • System distribution information • Duration of subsequent administration after exposure • Results, including the following aspects: – Nature and frequency of pharmacological or toxic effects — Severity or intensity of pharmacological or toxic effects — Time lysed to occurrence of effects — Reversibility of effects — Duration of effects — Response to response dose Table or above should be provided whenever possible in order to enhance the clarity of the presentation. The following sections should analyse the most important findings of the studies, including the ratio of the response to the dose of effects observed, their relevance and any aspect that should be studied in humans. Where appropriate, the findings should be compared with effective and non-toxic doses of species (i.e. the therapeutic index should be discussed). The relevance of this information to the proposed human dose should be appreciated. Where possible, blood or tissue levels should be compared without a ratio mg/kg to a pharmacological no Clinica A summary of the pharmacological aspects of the investigational medicinal product and, where appropriate, of the major metabolites studied in animals should be included. This summary should specify studies evaluating potential therapeutic activity (e.g. efficacy models, receptor binding and specificity) as well as safety assessment studies (e.g. specific studies to evaluate pharmacological effects other than those required). (b) Pharmacokinetics and metabolism of the medicinal product in animals Should include a summary of the metabolism and pharmacokinetic and biological elimination of the investigational drug in all species studied. The discussion of the findings should address the absorption and local and systemic bioavailability of the investigational drug and its metabolites, as well as its relationship to pharmacological and toxicological findings in animal species. (c) Toxicology Where appropriate, a summary of toxicological effects should be included in relevant studies in different animal species under the following titres: – Single dose — Repeated doses — Carcinogenesis — Specific studies (e.g. Irritability and sensitisation) — Reproductive toxicity — Genotoxicity (mutagensesis) 7.3.6 Effects on humans Introduction: A thorough discussion of the known effects of research medicinal products in humans should be facilitated, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided in response to the results of any use of research medicinal products outside clinical trials, such as experience during marketing. (a) Pharmacokinetics and metabolism of the medicinal product in humans A summary of information on the pharmacokinetics of the investigational medicinal product should be submitted, including, where available: – pharmacokinetics (including metabolism, where appropriate, and absorption, plasma protein joints, distribution and elimination). – Bioavailability of investigational medicinal products (absolute, if possible and/or relative) using the reference pharmaceutical form. – Population groups (e.g. by gender, age and change in organ function). – Interactions (e.g. drug interactions and the effect of co-administration with food). Other pharmacokinetic data (e.g. results of population studies clinical trials). (b) Safety and efficacy A summary of safety data, pharmacodynamics, efficacy as well as dose response studies of investigational medicinal products (including metabolites, if necessary) obtained in previous human studies (healthy volunteers and/or patients) should be provided. The consequences of this information should be analysed. In other clinical trials, the use of the summary of safety and efficacy of different studies by indication and subgroup will facilitate the understanding of the data. It would be useful to provide a tabulation of adverse reactions in all studies (including all indications studied). Important differences identified in models or incidence of adverse reactions in different indications or subgroups should be discussed. The RS should provide a description of the potential risks and expected RAM based on previous experience with research medicinal products and related medicinal products. Preventive measures or specific monitoring should also be described as part of the research into medicinal products. (c) Experience during the placing on the market of Mi should identify the countries where the investigational medicinal product is authorised or placed on the market. All relevant information resulting from the use of the product on the market should be summarised (e.g. pharmaceutical forms, doses, methods of administration and RAM). The MI shall also identify all countries where the investigational medicinal product has not been authorised for the placing on the market or marketing of the medicinal product or where the authorisation has been withdrawn. 7.3.7 Summary of data and guidance for the examiner. This section should include a comprehensive discussion of clinical and non-clinical data and, where possible, summarise information from different sources on the different aspects of the investigational drug. In this way, the researcher will have the best information on the available data and an evaluation of the implications of this information for future clinical trials. Where appropriate, published reports on related medicinal products should be discussed. These could help the researcher predict adverse drug reactions or other problems that may arise in a clinical trial. The overall objective of this section is to provide the investigator with a clear understanding of the potential risks and adverse reactions, as well as the specific tests, observations and precautions that may be necessary during the clinical trial. This knowledge should be based on available physical, chemical, pharmacological, pharmacological, toxicological and clinical information concerning the investigational medicinal product. Clinical researchers should also be provided with guidance on the recognition of tratamiento de posibles sobredosis y reacciones adversas al farmaco, basandose en la experiencia previa en humanos y en la farmacologia del medicamento en investigacion. 7.4 APENDICE 1: TITULO DE LA PAGINA (Ejemplo) NOMBRE DEL PROMOTOR Medicamento: Numero de Investigacion: Nombre: Quimico, Generico (si esta aprobado) Nombre Comercial (si esta permitido legalmente y lo desea el promotor) MANUAL DEL INVESTIGADOR NombreNumero de Edicion: Fecha de Edicion: Reemplaza al Numero de Edicion Front: Fecha: 7.5 APENDICE 2: INDICE DEL MANUAL DEL INVESTIGADOR (Ejemplo) — Declaracion de Confidencialidad (opcional) — Pagina de firmas (opcional) 1. Indice 2. Restore 3. Introduction 4. Propiedades Fisicas, Quimicas y Pharmaceuticals, y Formulaciones 5. Estudios no clinicos 5.1 Farmacologia No Clinica 5.2 Farmacocinetica y Metabolismo del Medicamento en animales 5.3 Toxicology 6. Efectos en Humanos 6. Resumen de datos y guia para el Investigador Nota: References sobre 1. Public administrations 2. Informs Se deberan encontrar estas referencias al final de cada capitulo. Apendices (you're a los haystack). Introduction The investigator's Brochure (IB) is a compilation of clinical and preclinical data on the investigational medicinal product(s) relevant for the study of the medicinal product(s) in humans. Its purpose is to provide investigators and other trial participants with information that will facilitate their understanding of the reasons and their adherence to many key elements of the protocol, such as dose, frequency/interval of doses, routes of administration: and safety monitoring procedures. IB also provides an overview to support the clinical management of study participants during the clinical trial. The information should be presented in a concise, simple, objective, balanced and non-promotional form that allows the doctor or potential investigator to understand them and carry out his own impartial risk-benefit assessment of the appropriateness of the proposed trial. Therefore, a person with medical qualifications should generally participate in adaptation IB, but the content of IB should be approved by the disciplines that produced the data described above. This Guideline shall define the minimum information to be included in IB and provide proposals for its organisation. It is expected that the type and extent of information available will vary depending on the stage of development of the product under investigation. If the investigational medicinal product is placed on the market and is generally understood by doctors in its pharmacology, extensive IB may not be necessary. If the regulatory authorities so permit, a brochure with basic product information, package leaflet or labelling may be a suitable alternative, provided that it contains up-to-date, comprehensive and detailed information on all aspects. product under test which could be of importance to the examiner. If a product placed on the market is being investigated for new uses (i.e. a new indication), an IB specific to this new use should be prepared. IB should be reviewed at least once a year and revised as necessary in accordance with the adjuthrator's written procedures. Depending on the stage of development and the production of relevant new information, a more frequent revision may be more appropriate. However, in accordance with good clinical practice, the relevant new information may be so important that it is communicated to the investigators and, where applicable, to the Institutional Review Committees (IEC)/Independent Ethics Committee (IEC) and/or regulatory authorities before it is included in the revised IB. The sponsor is generally responsible for ensuring that up-to-date IB is available to researchers and that investigators are responsible for providing up-to-date IB. In the case of a trial sponsored by a researcher, the sponsor-researcher should determine whether the brochure is available from a commercial manufacturer. If the test product is provided by a sponsor-researcher, then it should provide the necessary information to the test staff. In cases where the preparation of a formal IB is impractical, the investigator-examiner should provide as a substitute an extended section of background information in the test report containing at least the up-to-date information described in this Guideline. 7.2 IB's general considerations should include: 7.2.1 The name of the Site This should provide the name of the sponsor, the identity of each product under investigation (i.e. research number, chemical or approved generic name and trade name(s), if legally permissible and requested by the sponsor) and the date of issue. It is also proposed to provide an issue number and a reference to the number and date of issue it replaces. An example is given in Appendix 1. 7.2.2 Confidentiality Statement The sponsor may wish to include a statement ordering the examine/consignee to treat IB as a confidential document for exclusive information and use of the investigation team and the IRB/IEC. 7.3 The content of the IB investigative brochure should contain the following sections, each with literature references, if applicable: 7.3.1 Content The content example is given in Appendix 2 7.3.2 Summary A concise summary (preferably not exceeding two pages) should be provided highlighting the relevant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic and clinical information relevant to the clinical development stage of the investigational medicinal product. 7.3.3 Introduction A brief introductory statement should be provided containing the chemical name (and the common and trade name(s) if the product(s) under investigation is approved, all active the pharmacological class of the product(s) under investigation and its expected position within that class (e.g. benefits), the rationale for carrying out research on the product(s) under investigation and the presumed prophylactic, therapeutic or diagnostic indication(s). Finally, the introductory statement should provide a general approach to be followed when assessing the product under investigation. 7.3.4 The physical, chemical and pharmaceutical properties and formula A should provide a description of the substances of the product under investigation (including the chemical and/or structural formula(s)) and a brief summary of the relevant physical, chemical and pharmaceutical properties should be provided. In order to allow for appropriate precautions to be taken during the experiment, a description of the formulation(s) to be used, including excipients, should be provided and justified where clinically relevant. Instructions for storing and handling dosing forms should also be provided. Any structural similarities with other known compounds should be reported. 7.3.5 Preclinical studies Introduction: The results of all relevant studies on non-clinical pharmacology, toxicology, pharmacokinetics and metabolism of the products under investigation should be provided in an aggregated form. This summary should address the methodology used, the results and the discussion of the relevance of the findings for the therapeutic and potential adverse and unintended effects on humans investigated. The information provided may include, where appropriate: - Nature and frequency of pharmacological or toxic effects - Severity or intensity of pharmacological or toxic effects - Time to onset of effects - Reversibility of effects - Duration of effects - Dose response Test species Number and sex of animals in each group Unit dose (e.g. Milligram/kilogram (mg/kg)) Dosing interval Dosing route Duration of dosing Duration Of systemic distribution Duration of subsequent results after exposure Including the following aspects: Tabular format/lists should be used whenever possible to improve presentation clarity. The following sections should discuss the most important findings from studies, including the response of observed dose effects, relevance to humans and all aspects to be studied in humans. Where appropriate, effective and non-toxic dose findings in the same species should be compared (i.e. the therapeutic index should be discussed). The relevance of this information to the proposed human behavior should be addressed. Where possible, blood/tissue levels should be compared rather than mg/kg. (a) Preclinical pharmacology A summary of the pharmacological aspects of the products under investigation and, where appropriate, of its major metabolites studied in animals should be included. Such a summary should include studies assessing potential therapeutic activity (e.g. efficacy of binding to receptors and specificity) as well as those assessing safety (e.g. specific studies to assess pharmacological measures other than the intended therapeutic effect (effects).b) Pharmacokinetics and product metabolism in animals A summary of pharmacokinetics and biological transformation and disposition of investigational medicinal products in all species studied should be provided. The discussion of the findings should address the absorption and local and systemic bioavailability of the products and metabolites studied and their relationship to pharmacological and toxicological findings in animal species. (c) Toxicology Summary of toxicological effects surveyed in relevant studies conducted in different species should be described, where appropriate, in the following headings: 7.3.6 Effects on humans Introduction: A thorough discussion should be provided on the known effects of investigational medicinal products in humans, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided concerning the results of any use of the products tested other than in clinical trials, such as experience during marketing. (a) Pharmacokinetics and metabolism of products in humans. (b) Safety and efficacy Summary of safety information of the investigational medicinal product(s) (including metabolites, where appropriate) safety, pharmacodynamics, efficacy and dose response obtained from previous human studies (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where several clinical trials have been completed, the use of safety and efficacy summaries in several trials as indicated in subgroups may provide a clear presentation of the data. Tabulation summaries of adverse drug reactions would be useful for all clinical studies (including those for all indications studied). Important differences in models/incidences of adverse drug reactions between indications or subgroups should be discussed. IB should provide a description of the potential risks and adverse reactions to the medicinal product to be expected from previous experience with the medicinal product under investigation and the related medicinal product. A description of the preventive measures or specific monitoring to be carried out as part of the examination of the use of the product(s) should also be provided. (c) Experience with the placing on the market of bib should identify the countries in which the product under investigation has been placed on the market or approved. All relevant information resulting from the use of the product after placing it on the market (e.g. formulations, doses, routes of administration and adverse drug reactions) should be summarised. IB should also identify all countries where the product under investigation has not received approval/registration for the withdrawn from placing on the market/registration. 7.3.7 Summary of data and guidelines for the investigator This section should provide an overall debate on preclinical and clinical data and summarise information from different sources on the different aspects of the products tested where possible. In this way, investigators may be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, published reports on related products should be discussed. This could help the investigator anticipate adverse drug reactions or other problems in clinical trials. The overall objective of this section is to provide investigators with a clear understanding of the potential risks and adverse reactions and specific tests, observations and precautions that may be necessary for the clinical trial. This understanding should be based on available physical, chemical, pharmaceutical, pharmacological, toxicological and clinical information on the product(s) being tested. The clinical investigator should also be provided with guidance on the recognition and treatment of possible overdose and adverse drug reactions based on previous human experience and the pharmacology of the investigational medicinal product 7.4 APPENDIX 1: PAGE TITLE (Example) SPONSOR NAME Product: Research Number: Name(s): Chemical, General (if approved) Business name (if legally admissible and required by sponsor) Investigator's issue number: Date of issue: Replaces previous issue number: Date: 7.5 APPENDIX 2: CONTENTS OF THE INVESTIGATOR'S BROCHURE (Example) - Confidentiality statement (optional) ..... 1 Content ..... 2 Summary ..... 3 Introduction ..... 4 Physical, chemical and pharmaceutical properties and formulation ..... 5 Preclinical study ..... 5.1 Preclinical pharmacology ..... 5.2 Pharmacokinetics and metabolism of products in animals ..... 5.3 Toxicology ..... 6 Effects in humans 6.1 Pharmacokinetics and metabolism of products in humans ..... 6.2 Safety and efficacy ..... 6.3 Marketing experience ..... 7 Summary of data and guidelines for the investigator ..... NB: References to 1. Publications 2. Messages These references should be found at the end of each chapter Supplements (if any) Single dose carcinogenicity In special studies (e.g. Irritability and sensitisation) Reproductive toxicity Genotoxicity (mutagenicity) A summary of information on the pharmacokinetics of the investigational medicinal product(s) should be submitted, including, where available: pharmacokinetics (including metabolism, where appropriate, and absorption, plasma protein binding, distribution and elimination). Bioavailability of the products under investigation (absolute, if possible and/or relative) using the reference dosing formulation. Population subgroups (e.g. gender, age and impaired organ function). interactions (e.g. drug-product interactions and food effects). Other pharmacokinetic data (e.g. results of population studies conducted in clinical trials). Introduction The investigator's Brochure (IB) is a compilation of clinical and non-clinical data on the investigational

medicinal product(s) relevant for the study of the medicinal product(s) in humans. Its purpose is to provide investigators and other trial participants with information that will facilitate their understanding of the reasons and their adherence to many key elements of the protocol, such as dose, frequency/interval of doses, routes of administration: and safety monitoring procedures. IB also provides an overview to support the clinical management of study participants during the clinical trial. The information should be presented in a concise, simple, objective, balanced and non-promotional form that allows the doctor or potential investigator to understand them and carry out his own impartial risk-benefit assessment of the appropriateness of the proposed trial. Therefore, a person with medical qualifications should generally participate in adaptation IB, but the content of IB should be approved by the disciplines that produced the data described above. This Guideline shall define the minimum information to be included in IB and provide proposals for its organisation. It is expected that the type and extent of information available will vary depending on the stage of development of the product under investigation. If the investigational medicinal product is placed on the market and is generally understood by doctors in its pharmacology, extensive IB may not be necessary. If the regulatory authorities so permit, a brochure with basic product information, a package leaflet or a may be an appropriate alternative, provided that it contains current, comprehensive and detailed information on all aspects of the examiner's product which might be relevant to the examiner. If a product placed on the market is being investigated for new uses (i.e. a new indication), an IB specific to this new use should be prepared. IB should be reviewed at least once a year and revised as necessary in accordance with the adjuthrator's written procedures. Depending on the stage of development and the production of relevant new information, a more frequent revision may be more appropriate. However, in accordance with good clinical practice, the relevant new information may be so important that it is communicated to the investigators and, where applicable, to the Institutional Review Committees (IEC)/Independent Ethics Committee (IEC) and/or regulatory authorities before it is included in the revised IB. The sponsor is generally responsible for ensuring that up-to-date IB is available to researchers and that investigators are responsible for providing up-to-date IB. In the case of a trial sponsored by a researcher, the sponsor-researcher should determine whether the brochure is available from a commercial manufacturer. If the test product is provided by a sponsor-researcher, then it should provide the necessary information to the test staff. 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The information provided may include, where appropriate: - Nature and frequency of pharmacological or toxic effects - Severity or intensity of pharmacological or toxic effects - Time to onset of effects - Reversibility of effects - Duration of effects - Dose response Test species Number and sex of animals in each group Unit dose (e.g. Milligram/kilogram (mg/kg)) Dosing interval Dosing route Duration of dosing Duration Of systemic distribution Duration of subsequent results after exposure Including the following aspects: Tabular format/lists should be used whenever possible to improve presentation clarity. The following sections should discuss the most important findings from studies, including the response of observed dose effects, relevance to humans and all aspects to be studied in humans. Where appropriate, effective and non-toxic dose findings in the same species should be compared (i.e. the therapeutic index should be discussed). The relevance of this information to the proposed human behavior should be addressed. Where possible, blood/tissue levels should be compared rather than mg/kg. (a) Preclinical pharmacology Summary of the pharmacological aspects of the products under investigation and, where appropriate, of its significant metabolites should be included. Such a summary should include studies assessing potential therapeutic activity (e.g. efficacy models, receptor binding and specificity) as well as safety assessment studies (e.g. specific studies to assess pharmacological measures other than the intended therapeutic effects). (b) Pharmacokinetics and metabolism of products in animals A summary of the pharmacokinetics and biological transformation and disposition of investigational medicinal products in all species studied should be provided. The discussion of the findings should address the absorption and local and systemic bioavailability of the products and metabolites studied and their relationship to pharmacological and toxicological findings in animal species. (c) Toxicology Summary of toxicological effects surveyed in relevant studies conducted in different species should be described, where appropriate, in the following headings: 7.3.6 Effects on humans Introduction: A thorough discussion should be provided on the known effects of investigational medicinal products in humans, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided concerning the results of any use of the products tested other than in clinical trials, such as experience during marketing. (a) Pharmacokinetics and metabolism of products in humans. (b) Safety and efficacy Summary of safety information of the investigational medicinal product(s) (including metabolites, where appropriate) safety, pharmacodynamics, efficacy and dose response obtained from previous human studies (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where several clinical trials have been completed, the use of safety and efficacy summaries in several trials as indicated in subgroups may provide a clear presentation of the data. Tabulation summaries of adverse drug reactions would be useful for all clinical studies (including those for all indications studied). Important differences in models/incidences of adverse drug reactions between indications or subgroups should be discussed. IB should provide a description of the potential risks and adverse reactions to the medicinal product to be expected from previous experience with the medicinal product under investigation and the related medicinal product. A description of the preventive measures or specific monitoring to be carried out as part of the examination of the use of the product(s) should also be provided. (c) Experience with the placing on the market of bib should identify the countries in which the product under investigation has been placed on the market or approved. All relevant information resulting from the use of the product after placing it on the market (e.g. formulations, doses, routes of administration and adverse drug reactions) should be summarised. IB should also identify all countries where the product under investigation has not received a marketing authorisation/registration or has been withdrawn from placing on the market/registration. 7.3.7 Summary of data and guidelines for the investigator This section should provide an overall debate on preclinical and clinical data and summarise information from different sources on the different aspects of the products tested where possible. In this way, investigators may be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, published reports on related products should be discussed. This could help the investigator anticipate adverse drug reactions or other problems in clinical trials. The overall objective of this section is to provide investigators with a clear understanding of the potential risks and adverse reactions and specific tests, observations and precautions that may be necessary for the clinical trial. This understanding should be based on available physical, chemical, pharmaceutical, pharmacological, toxicological and clinical information on the product(s) being tested. The clinical investigator should also be provided with guidance on the recognition and treatment of possible overdose and adverse drug reactions based on previous human experience and the pharmacology of the investigational medicinal product 7.4 APPENDIX 1: PAGE TITLE (Example) SPONSOR NAME Product: Research Number: Name(s): Chemical, General (if approved) Business name (if legally admissible and required by sponsor) Investigator's issue number: Date of issue: Replaces previous issue number: Date: 7.5 APPENDIX 2: CONTENTS OF THE INVESTIGATOR'S BROCHURE (Example) - Confidentiality statement (optional) ..... 1 Content ..... 2 Summary ..... 3 Introduction ..... 4 Physical, chemical and pharmaceutical properties and formulation ..... 5 Preclinical study ..... 5.1 Preclinical pharmacology ..... 5.2 Pharmacokinetics and metabolism of products in animals ..... 5.3 Toxicology ..... 6 Effects in humans ..... 6.1 Pharmacokinetics and metabolism of products in humans ..... 6.2 Safety and efficacy ..... 6.3 Marketing experience ..... 7 Summary of data and guidelines for the investigator ..... NB: References to 1. Publications 2. Messages These references should be found at the end of each chapter Supplements (if any) Single dose carcinogenicity In special studies (e.g. Irritability and sensitisation) Reproductive toxicity Genotoxicity (mutagenicity) A summary of information on the pharmacokinetics of the investigational medicinal product(s) should be submitted, including, where available: pharmacokinetics (including metabolism, where appropriate, and absorption, plasma protein binding, distribution and elimination). Bioavailability of the products under investigation (absolute, if possible and/or relative) using the reference dosing formulation. Population subgroups (e.g. gender, age and impaired organ function). interactions (e.g. drug-product interactions and food effects). Other pharmacokinetic data (e.g. results of population studies conducted in clinical trials). Introduction The investigator's Brochure (IB) is a compilation of clinical and non-clinical data on the investigational medicinal product(s) relevant for the study of the medicinal product(s) in humans. Its purpose is to provide investigators and other trial participants with information that will facilitate their understanding of the reasons and their adherence to many key elements of the protocol, such as dose, frequency/interval of doses, routes of administration: and safety monitoring procedures. IB also provides an overview to support the clinical management of study participants during the clinical trial. The information should be presented in a concise, simple, objective, balanced and non-promotional form that allows the doctor or potential investigator to understand them and carry out his own impartial risk-benefit assessment of the appropriateness of the proposed trial. Therefore, a person with medical qualifications should generally participate in adaptation IB, but the content of IB should be approved by the disciplines that produced the data described above. This Guideline shall define the minimum information to be included in IB and provide proposals for its organisation. It is expected that the type and extent of information available will vary depending on the stage of development of the product under investigation. If the investigational medicinal product is placed on the market and is generally understood by doctors in its pharmacology, may not be necessary. If the regulatory authorities so permit, a brochure with basic product information, package leaflet or labelling may be a suitable alternative, provided that it contains current, comprehensive and detailed information on all aspects of the examiner's product that might be relevant to the examiner. If a product placed on the market is being investigated for new uses (i.e. a new indication), an IB specific to this new use should be prepared. IB should be reviewed at least once a year and revised as necessary in accordance with the adjuthrator's written procedures. Depending on the stage of development and the production of relevant new information, a more frequent revision may be more appropriate. However, in accordance with good clinical practice, the relevant new information may be so important that it is communicated to the investigators and, where applicable, to the Institutional Review Committees (IEC)/Independent Ethics Committee (IEC) and/or regulatory authorities before it is included in the revised IB. The sponsor is generally responsible for ensuring that up-to-date IB is available to researchers and that investigators are responsible for providing up-to-date IB. In the case of a trial sponsored by a researcher, the sponsor-researcher should determine whether the brochure is available from a commercial manufacturer. If the test product is provided by a sponsor-researcher, then it should provide the necessary information to the test staff. In cases where the preparation of a formal IB is impractical, the investigator-examiner should provide as a substitute an extended section of background information in the test report containing at least the up-to-date information described in this Guideline. 7.2 IB's general considerations should include: 7.2.1 The name of the Site This should provide the name of the sponsor, the identity of each product under investigation (i.e. research number, chemical or approved generic name and trade name(s), if legally permissible and requested by the sponsor) and the date of issue. It is also proposed to provide an issue number and a reference to the number and date of issue it replaces. An example is given in Appendix 1. 7.2.2 Confidentiality Statement The sponsor may wish to include a statement ordering the examine/consignee to treat IB as a confidential document for exclusive information and use of the investigation team and the IRB/IEC. 7.3 The content of the IB investigative brochure should contain the following sections, each with literature references, if applicable: 7.3.1 Content The content example is given in Appendix 2 7.3.2 Summary A brief summary (preferably not exceeding two pages) should be provided highlighting the relevant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic and clinical information relevant to the development of the investigational medicinal product. 7.3.3 Introduction A brief introductory statement should be provided containing the chemical name (and the common and trade name(s) if all active substances are approved, the pharmacological substance(s) of the investigational medicinal product(s) and its expected position in this class (e.g. benefits), the rationale for carrying out research on the products under investigation and the presumed prophylactic, therapeutic or diagnostic indication(s). Finally, the introductory statement should provide a general approach to be followed when assessing the product under investigation. 7.3.4 The physical, chemical and pharmaceutical properties and formula A should provide a description of the substances of the product under investigation (including the chemical and/or structural formula(s)) and a brief summary of the relevant physical, chemical and pharmaceutical properties should be provided. In order to allow for appropriate precautions to be taken during the experiment, a description of the formulation(s) to be used, including excipients, should be provided and justified where clinically relevant. Instructions for storing and handling dosing forms should also be provided. Any structural similarities with other known compounds should be reported. 7.3.5 Preclinical studies Introduction: The results of all relevant studies on non-clinical pharmacology, toxicology, pharmacokinetics and metabolism of the products under investigation should be provided in an aggregated form. This summary should address the methodology used, the results and the discussion of the relevance of the findings for the therapeutic and potential adverse and unintended effects on humans investigated. The information provided may include, where appropriate: - Nature and frequency of pharmacological or toxic effects - Severity or intensity of pharmacological or toxic effects - Time to onset of effects - Reversibility of effects - Duration of effects - Dose response Test species Number and sex of animals in each group Unit dose (e.g. Milligram/kilogram (mg/kg)) Dosing interval Dosing route Duration of dosing Duration Of systemic distribution Duration of subsequent results after exposure Including the following aspects: Tabular format/lists should be used whenever possible to improve presentation clarity. The following sections should discuss the most important findings from studies, including the response of observed dose effects, relevance to humans and all aspects to be studied in humans. Where appropriate, effective and non-toxic dose findings in the same species should be compared (i.e. the therapeutic index should be discussed). The relevance of this information to the proposed human behavior should be addressed. Where possible, blood/tissue levels should be compared rather than mg/kg. (a) Preclinical pharmacology a summary of the pharmacological aspects of the products under investigation and, where appropriate, of its relevant metabolites studied in animals. Such a summary should include studies assessing potential therapeutic activity (e.g. efficacy models, receptor binding and specificity) as well as safety assessment studies (e.g. specific studies to assess pharmacological measures other than the intended therapeutic effects). (b) Pharmacokinetics and metabolism of products in animals A summary of the pharmacokinetics and biological transformation and disposition of investigational medicinal products in all species studied should be provided. The discussion of the findings should address the absorption and local and systemic bioavailability of the products and metabolites studied and their relationship to pharmacological and toxicological findings in animal species. (c) Toxicology Summary of toxicological effects surveyed in relevant studies conducted in different species should be described, where appropriate, in the following headings: 7.3.6 Effects on humans Introduction: A thorough discussion should be provided on the known effects of investigational medicinal products in humans, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided concerning the results of any use of the products tested other than in clinical trials, such as experience during marketing. (a) Pharmacokinetics and metabolism of products in humans. (b) Safety and efficacy Summary of safety information of the investigational medicinal product(s) (including metabolites, where appropriate) safety, pharmacodynamics, efficacy and dose response obtained from previous human studies (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where several clinical trials have been completed, the use of safety and efficacy summaries in several trials as indicated in subgroups may provide a clear presentation of the data. Tabulation summaries of adverse drug reactions would be useful for all clinical studies (including those for all indications studied). Important differences in models/incidences of adverse drug reactions between indications or subgroups should be discussed. IB should provide a description of the potential risks and adverse reactions to the medicinal product to be expected from previous experience with the medicinal product under investigation and the related medicinal product. A description of the preventive measures or specific monitoring to be carried out as part of the examination of the use of the product(s) should also be provided. (c) Experience in marketing IB should be the countries in which the product under investigation has been sold or approved. All relevant information resulting from the use of the product after placing it on the market (e.g. formulations, doses, routes of administration and adverse drug reactions) should be summarised. IB should also identify all countries where the product under investigation has not received a marketing authorisation/registration or has been withdrawn from placing on the market/registration. 7.3.7 Summary of data and guidelines for the investigator This section should provide an overall debate on preclinical and clinical data and summarise information from different sources on the different aspects of the products tested where possible. In this way, investigators may be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, published reports on related products should be discussed. This could help the investigator anticipate adverse drug reactions or other problems in clinical trials. The overall objective of this section is to provide investigators with a clear understanding of the potential risks and adverse reactions and specific tests, observations and precautions that may be necessary for the clinical trial. This understanding should be based on available physical, chemical, pharmaceutical, pharmacological, toxicological and clinical information on the product(s) being tested. 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NB: References to 1. Publications 2. Messages These references should be found at the end of each chapter Supplements (if any) Single dose carcinogenicity In special studies (e.g. Irritability and sensitisation) Reproductive toxicity Genotoxicity (mutagenicity) A summary of information on the pharmacokinetics of the investigational medicinal product(s) should be submitted, including, where available: pharmacokinetics (including metabolism, where appropriate, and absorption, plasma protein binding, distribution and elimination). Bioavailability of the products under investigation (absolute, if possible and/or relative) using the reference dosing formulation. Population subgroups (e.g. gender, age and impaired organ function). interactions (e.g. drug-product interactions and food effects). Other pharmacokinetic data (e.g. results of population studies conducted in clinical trials). Page 9 7.1 Introduction Investigator documentation (IB) and set of clinical and non-clinical data on the test product(s) relevant for the study of the medicinal product(s) in humans. Its purpose is to provide investigators and persons involved in the clinical trial with information that facilitates understanding of protocol principles and adherence to several key factors of the protocol, such as dosage, frequency/interval of doses, routes of administration and procedures for monitoring product safety. IB is also a knowledge-based tool for clinical subject management during the study. The information shall be presented in a concise, simple, objective, balanced and non-promotional form that allows the physician or potential investigator to clearly understand and impartially assue the suitability of the proposed study from the risk-benefit ratio. For this reason, a person with medical qualifications usually has to participate in the development of IB, the content of which must also be approved by experts in the various disciplines which provided the data. This Guideline the minimum information to be included in the IU which provides proposals for its development. It is assumed that the type and extent of information available may vary in relation to the development phase of the product under investigation. A large-scale IB may not be necessary if the medicine is well known in the study and on the market and its pharmacology is well known in the medical class. Where the regulatory authorities so permit, the basic product information documentation, package leaflet or label may be a viable alternative, provided that it contains up-to-date, comprehensive and detailed information on all aspects of the products under investigation which may be relevant to the examiner. If the product is to be designed for a new use on the market (i.e. a new labelling), specification IB for the proposed new use must be prepared. IB shall be reviewed at least once a year and, if necessary, reviewed in accordance with the adjuthrator's written procedures. More frequent examination may be appropriate in relation to the product development phase or where relevant new information is available. However, in accordance with good clinical practice, new relevant information may be so important that it must be communicated to investigators and, where appropriate, to the Institutional Audit Committees (IRB)/Independent Ethics Committee (IEC) and/or regulatory authorities before it is included in the revised IB. @include(advertisements.content.1) In general and responsible for sponsorship, it shall ensure that update IB is made available to the investigator(s) and investigators' responsibility for providing the updated IB IRB/IEC responsible for the study. Where the study is promoted by the investigator, the sponsor-researcher shall ensure that he has the product documentation provided by the commercial manufacturer If the product in the study and provided by the sponsoring investigator, the sponsor must provide the necessary information to the personnel involved in the experiment. If the preparation of formal IB is inoperative, the investigator shall extend instead of IB the section of the clinical protocol concerning retrospective information containing minimal, up-to-date information described in this Guideline. 7.2 IB's general considerations must include: 7.2.1 The front page this must include the sponsor's name, the identification of the product in the studio (e.g. experimental abbreviation, approved chemical name or generic name and trade name, if permitted by law or required by the sponsor) and the date of distribution. It is also recommended that you report a progressive release number and replace the reference to the number and date of the previous release. Example and listed in Appendix 1. 7.2.2. 7.3 The content of the investigator's IB dossier contains the following sections, each with bibliographic references where appropriate: 7.3.1 Index example of index and listed in Appendix 2. 7.3.2 Summary To highlight available and significant physico-chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic and clinical data relevant to the clinical development phase of the test product, a short summary (preferably not more than two pages) should be provided. 7.3.3 Introduction Short introductory paragraph containing the chemical name (and common and trade name, if approved) of the product(s) in the study, all active substances, the pharmacological class of the product(s) and its intended class placement (e.g. benefits), the rationale for carrying out research on the product(s) concerned and the expected prophylactic, therapeutic or diagnostic indications. Finally, the introduction should provide a general guidance to be followed in the evaluation of the medicinal product in the study. 7.3.4 Composition and physico-chemical and pharmaceutical properties A description of the substance(s) in the study (including the chemical and/or structural formula) and a brief summary of the physico-physical and pharmaceutical properties relating to the substance shall be provided. In order to take appropriate precautions during the experiment, the formulation(s) to be used, including ecipions, should be described and justified, where clinically relevant. Instructions should also be given on the storage and use of the pharmaceutical form(s). All structural analogues with other known compounds should be reported. 7.3.5 Preclinical studies Introduction: The results of all relevant preclinical pharmacological, toxicological, pharmacokinetic and metabolic studies of the investigational medicinal product should be summarised. This summary should cover the methodology used, the results and discuss the relevance between the data obtained and the therapeutic effects in the study and possible adverse and adverse effects on humans. The information to be provided may include, where appropriate, the following data, if known/available: • species tested • number and sex of animals in each group • dose unit (e.g. mg/kg) • dose range • route of administration • duration of treatment • information on systemic distribution • duration of post-exposure control • results including the following aspects: – nature and frequency of pharmacological or toxic effects – gravity or pharmacological or toxic effects – time of onset of effects – reversible effects – duration of effects – dose-response relationship. Where possible, the information must be summarised in the form of tables or tables to make the presentation clearer. The following sections should illustrate the most important results of studies, including the dose-response relationship of observed effects, human significance and all aspects to be studied in humans. Where appropriate, the results of the effective and non-toxic dose should be compared with the same animal species (e.g. the therapeutic index should be discussed). The relevance between this information and the proposed human dose should be treated. Where possible, a comparison should be made in terms of plasma/tissue levels rather than mg/kg. (a) Non-clinical pharmacology A summary of the pharmacological aspects of the products under investigation and, where appropriate, of its major metabolites studied in animals should be included. This summary should include studies identifying potential therapeutic activity (e.g. efficacy models, receptor binding and specific) and safety studies (e.g. specific studies to detect pharmacological effects in addition to the desired therapeutic effects). (b) Pharmacokinetics and metabolism in animals Pharmacokinetics, metabolism and elimination data of the investigational medicinal product in all species studied shall be summarised. The discussion of the

data obtained should concern the absorption and local and systemic bioavailability of the medicinal product in the study and its metabolites and their relationship to pharmacological and toxicological data in animal species. (c) Toxicological toxicological effects obtained from studies carried out in different animal species should be summarised and described, where appropriate, in relation to: – single dose – repeated dose – carcinogens – specific studies (e.g. Studies on phenomena of irritation and sensitisation) — Toxicity for reproduction — Genotoxic (mutagensesis) 7.3.6 Effects in humans Introduction: An in-depth discussion should be presented on the known effects of the investigational medicinal product(s) in man, including information on pharmacokinetics, metabolism, pharmacodynamics, dose-response relationship, safety, efficacy and other pharmacological activities. Where possible, a summary of any clinical trial already completed should be provided. In addition to the information obtained from clinical trials, information resulting from any use of the medicinal product(s) in the study, such as data obtained from the placing on the market of the medicinal product, shall be provided. (a) Pharmacokinetics and metabolism in humans – The study should provide a summary of the pharmacokinetics of the medicinal product(s) containing, if available, the following data: – (including metabolism, where appropriate, and absorption, plasma protein binding, distribution and elimination). – Bioavailability of the product in the study (absolute, if possible and/or relative) using the reference pharmaceutical form. – Subgroups of populations (e.g. gender, age and altered organic functionality). – Interactions (e.g. drug-to-drug interactions and food interactions). – Other pharmacokinetic data (e.g. results of population studies conducted in clinical trials). (b) Safety and efficacy A summary of the safety data of the medicinal product(s) in the study (including data on metabolites, where appropriate), pharmacodynamics, efficacy and dose-response relationship, obtained from previous human studies (healthy volunteers and/or patients) should be provided. The implications of this information need to be discussed. In cases where several clinical trials have been completed, a clear presentation of the data may consist of the use of safety and efficacy summaries for different trials divided into subgroups according to indications. Summary tables of adverse drug reactions will be useful for all clinical studies (including those performed on all other indications studied). Important differences in the structure/incidence of adverse drug reactions via indications or subgroups should be discussed. IB should provide a description of the potential risks and adverse drug reactions that can be anticipated from previous experience with the investigational medicinal product or associated medicinal products. A description of the precautionary measures to be taken or of the specific monitoring to be carried out in experimental use of the product(s.c) The marketing experience with the IB product must indicate the countries where the product was approved in the study or on the market. All relevant information obtained from the placing on the market of the product should be summarised (e.g. formulations, doses, routes of administration, adverse drug reactions). IB must also indicate all countries in which the product has not been approved/registered for placing on the market or has been withdrawn from trade or withdrawn. 7.3.7 Summary of data and investigator's manual This section should present a general discussion of clinical and non-clinical data and, where possible, summarise information from different sources on the different aspects of the medicinal product(s) in the study. In this way, the investigator may have the most comprehensive interpretation of the available data and an assessment of the implications for future clinical trials. Where appropriate, published reports concerning related products should be discussed. This may be to assist the investigator in predicting other problems during clinical studies. The overall purpose of this section is to provide the investigator with the means to clearly assess possible risks and adverse reactions, as well as the specific tests, observations and precautions that may be necessary to conduct the clinical trial. This assessment is based on available physico-chemical, pharmaceutical, pharmacological, toxicological and clinical information concerning the investigational medicinal product. Investigators shall also be provided with information to be followed in the recognition and treatment of all cases of overdose and adverse drug reactions based on previous human experience and the pharmacological properties of the investigational medicinal product. 7.4 APPENDIX 1: COVER PAGE (Example) SPONSOR NAME Product: Experimental code: Name: Chemical name, generic name (if approved) Trade name (if legally permitted and if required by sponsor) EXPERIMENTAL DOCUMENTATION Issue number: Date of publication: Replace previous release Number: Date: 7.5 APPENDIX 2: EXPERIMENTAL DOCUMENTATION INDEX (Example) – Confidentiality (optional) – Signature page (optional) 1 Summary 1. Introduction 4 Formulation and properties Physico-chemical and pharmaceutical 5 Non-clinical studies 5.1 Non-clinical pharmacology 5.2 Pharmacokinetics and metabolism in animals 5.3 Toxicology 6 Effects in humans 6. Publications 2. Messages References should be inserted at the end of each chapter Appendices (if any) Page 10 7.1 Introduction Investigator documentation (IB) is a compilation of clinical and non-clinical data on the investigational medicinal product(s) relevant for the study of the medicinal product(s) in humans. Its purpose is to provide investigators and other trial participants with information that will facilitate their understanding of the reasons and their adherence to many key elements of the protocol, such as dose, frequency/interval of doses, routes of administration: and safety monitoring procedures. IB also provides an overview to support the clinical management of study participants during the clinical trial. The information should be presented in a concise, simple, objective, balanced and non-promotional form that allows the doctor or potential investigator to understand them and carry out his own impartial risk-benefit assessment of the appropriateness of the proposed trial. Therefore, a person with medical qualifications should generally participate in adaptation IB, but the content of IB should be approved by the disciplines that produced the data described above. This Guideline sets out the minimum information IB and provides proposals for its organisation. It is expected that the type and extent of information available will vary depending on the stage of development of the product under investigation. If the investigational medicinal product is placed on the market and is generally understood by doctors in its pharmacology, extensive IB may not be necessary. If the regulatory authorities so permit, a brochure with basic product information, package leaflet or labelling may be a suitable alternative, provided that it contains current, comprehensive and detailed information on all aspects of the examiner's product that might be relevant to the examiner. If a product placed on the market is being investigated for new uses (i.e. a new indication), an IB specific to this new use should be prepared. IB should be reviewed at least once a year and revised as necessary in accordance with the adjuthrator's written procedures. Depending on the stage of development and the production of relevant new information, a more frequent revision may be more appropriate. However, in accordance with good clinical practice, the relevant new information may be so important that it is communicated to the investigators and, where applicable, to the Institutional Review Committees (IEC)/Independent Ethics Committee (IEC) and/or regulatory authorities before it is included in the revised IB. The sponsor is generally responsible for ensuring that up-to-date IB is available to researchers and that investigators are responsible for providing up-to-date IB. In the case of a trial sponsored by a researcher, the sponsor-researcher should determine whether the brochure is available from a commercial manufacturer. If the test product is provided by a sponsor-researcher, then it should provide the necessary information to the test staff. In cases where the preparation of a formal IB is impractical, the investigator-examiner should provide as a substitute an extended section of background information in the test report containing at least the up-to-date information described in this Guideline. 7.2 IB's general considerations should include: 7.2.1 The name of the Site This should provide the name of the sponsor, the identity of each product under investigation (i.e. research number, chemical or approved generic name and trade name(s), if legally permissible and requested by the sponsor) and the date of issue. It is also proposed to provide an issue number and a reference to the number and date of issue it replaces. An example is given in Appendix 1. 7.2.2 Confidentiality Statement The sponsor may wish to include a statement ordering the examine/consignee to treat IB as a confidential document for exclusive information and use of the investigation team and the IRB/IEC. 7.3 The content of the investigator's IB dossier should contain the following sections, each with literature references where appropriate: 7.3.1 Content An example of the content is given in Appendix 2 7.3.2 Summary A brief summary (preferably not exceeding two pages) should be provided highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic and clinical information relevant to the clinical development stage of the test substance. 7.3.3 Introduction A brief introductory statement should be provided containing the chemical name (and the common and trade name(s) if all active substances are approved, the pharmacological substance(s) of the investigational medicinal product(s) and its expected position in this class (e.g. benefits), the rationale for carrying out research on the products under investigation and the presumed prophylactic, therapeutic or diagnostic indication(s). Finally, the introductory statement should provide a general approach to be followed when assessing the product under investigation. 7.3.4 The physical, chemical and pharmaceutical properties and formula A should provide a description of the substances of the product under investigation (including the chemical and/or structural formula(s)) and a brief summary of the relevant physical, chemical and pharmaceutical properties should be provided. In order to allow for appropriate precautions to be taken during the experiment, a description of the formulation(s) to be used, including excipients, should be provided and justified where clinically relevant. Instructions for storing and handling dosing forms should also be provided. Any structural similarities with other known compounds should be reported. 7.3.5 Preclinical studies Introduction: The results of all relevant studies on non-clinical pharmacology, toxicology, pharmacokinetics and metabolism of the products under investigation should be provided in an aggregated form. This summary should address the methodology used, the results and the discussion of the relevance of the findings for the therapeutic and potential adverse and unintended effects on humans investigated. The information provided may include, where appropriate: - Nature and frequency of pharmacological or toxic effects - Severity or intensity of pharmacological or toxic effects - Time to onset of effects - Reversibility of effects - Duration of effects - Dose response Test species Number and sex of animals in each group Unit dose (e.g. Milligram/kilogram (mg/kg)) Dosing interval Dosing route Duration of dosing Duration Of systemic distribution Duration of subsequent results after exposure Including the following aspects: Tabular format/lists should be used whenever possible to improve presentation clarity. The following sections should discuss the most important findings from studies, including the response of observed dose effects, relevance to humans and all aspects to be studied in humans. Where appropriate, an effective and non-toxic dose species (i.e. the therapeutic index should be discussed). The relevance of this information to the proposed human behavior should be addressed. Where possible, blood/tissue levels should be compared rather than mg/kg. (a) Preclinical pharmacology A summary of the pharmacological aspects of the products under investigation and, where appropriate, of its major metabolites studied in animals should be included. Such a summary should include studies assessing potential therapeutic activity (e.g. efficacy models, receptor binding and specificity) as well as safety assessment studies (e.g. specific studies to assess pharmacological measures other than the intended therapeutic effects). (b) Pharmacokinetics and metabolism of products in animals A summary of the pharmacokinetics and biological transformation and disposition of investigational medicinal products in all species studied should be provided. The discussion of the findings should address the absorption and local and systemic bioavailability of the products and metabolites studied and their relationship to pharmacological and toxicological findings in animal species. (c) Toxicology Summary of toxicological effects surveyed in relevant studies conducted in different species should be described, where appropriate, in the following headings: 7.3.6 Effects on humans Introduction: A thorough discussion should be provided on the known effects of investigational medicinal products in humans, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided concerning the results of any use of the products tested other than in clinical trials, such as experience during marketing. (a) Pharmacokinetics and metabolism of products in humans. (b) Safety and efficacy Summary of safety information of the investigational medicinal product(s) (including metabolites, where appropriate) safety, pharmacodynamics, efficacy and dose response obtained from previous human studies (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where several clinical trials have been completed, the use of safety and efficacy summaries in several trials as indicated in subgroups may provide a clear presentation of the data. Tabulation summaries of adverse drug reactions would be useful for all clinical studies (including those for all indications studied). Important differences in models/incidences of adverse drug reactions between indications or subgroups should be discussed. IB should be a description of the potential risks and adverse reactions to the medicinal product to be expected from previous experience with the product under investigation and the related medicinal product. A description of the preventive measures or specific monitoring to be carried out as part of the examination of the use of the product(s) should also be provided. (c) Experience with the placing on the market of bib should identify the countries in which the product under investigation has been placed on the market or approved. All relevant information resulting from the use of the product after placing it on the market (e.g. formulations, doses, routes of administration and adverse drug reactions) should be summarised. IB should also identify all countries where the product under investigation has not received a marketing authorisation/registration or has been withdrawn from placing on the market/registration. 7.3.7 Summary of data and guidelines for the investigator This section should provide an overall debate on preclinical and clinical data and summarise information from different sources on the different aspects of the products tested where possible. In this way, investigators may be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, published reports on related products should be discussed. This could help the investigator anticipate adverse drug reactions or other problems in clinical trials. The overall objective of this section is to provide investigators with a clear understanding of the potential risks and adverse reactions and specific tests, observations and precautions that may be necessary for the clinical trial. This understanding should be based on available physical, chemical, pharmaceutical, pharmacological, toxicological and clinical information on the product(s) being tested. 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Therefore, a person with medical qualifications should generally participate in adaptation IB, but the content of IB should be approved by the disciplines that produced the data described above. This Guideline shall define the minimum information to be included in IB and provide proposals for its organisation. It is expected that the type and extent of information available will vary depending on the stage of development of the product under investigation. If the investigational medicinal product is placed on the market and is generally understood by doctors in its pharmacology, extensive IB may not be necessary. If the regulatory authorities so permit, a brochure with basic product information, package leaflet or labelling may be a suitable alternative, provided that it contains current, comprehensive and detailed information on all aspects of the examiner's product that might be relevant to the examiner. If a product placed on the market is being investigated for new uses (i.e. a new indication), an IB specific to this new use should be prepared. IB should be reviewed at least once a year and revised as necessary in accordance with the adjuthrator's written procedures. Depending on the stage of development and the production of relevant new information, a more frequent revision may be more appropriate. However, in accordance with good clinical practice, the relevant new information may be so important that it is communicated to the investigators and, where applicable, to the Institutional Review Committees (IEC)/Independent Ethics Committee (IEC) and/or regulatory authorities before it is included in the revised IB. The sponsor is generally responsible for ensuring that up-to-date IB is available to researchers and that investigators are responsible for providing up-to-date IB. 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Finally, the introductory statement should provide a general approach to be followed when assessing the product under investigation. 7.3.4 The physical, chemical and pharmaceutical properties and formula A should provide a description of the substances of the product under investigation (including the chemical and/or structural formula(s)) and a brief summary of the relevant physical, chemical and pharmaceutical properties should be provided. In order to allow for appropriate precautions to be taken during the experiment, a description of the formulation(s) to be used, including excipients, should be provided and justified where clinically relevant. Instructions for storing and handling dosing forms should also be provided. 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Information provided may include, where appropriate: - Nature and frequency of pharmacological or toxic effects - Severity or intensity of pharmacological or toxic effects - Time to onset of effects - Reversibility of effects - Duration of effects - Dose response Test species Number and sex of animals in each group Unit dose (e.g. milligram/kilogram (mg/kg)) Dosing interval Route Submission Duration of annual submission Information on systemic distribution Duration of subsequent results after exposure Including the following aspects: Tabular format/lists should be used whenever possible to improve the clarity of the presentation. The following sections should discuss the most important findings from studies, including the response of observed dose effects, relevance to humans and all aspects to be studied in humans. Where appropriate, effective and non-toxic dose findings in the same species should be compared (i.e. the therapeutic index should be discussed). The relevance of this information to the proposed human behavior should be addressed. Where possible, blood/tissue levels should be compared rather than mg/kg. (a) Preclinical pharmacology A summary of the pharmacological aspects of the products under investigation and, where appropriate, of its major metabolites studied in animals should be included. Such a summary should include studies assessing potential therapeutic activity (e.g. efficacy models, receptor binding and specificity) as well as safety assessment studies (e.g. specific studies to assess pharmacological measures other than the intended therapeutic effects). (b) Pharmacokinetics and metabolism of products in animals A summary of the pharmacokinetics and biological transformation and disposition of investigational medicinal products in all species studied should be provided. 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In this way, investigators may be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, published reports on related products should be discussed. This could help the investigator anticipate adverse drug reactions or other problems in clinical trials. The overall objective of this section is to provide investigators with a clear understanding of the potential risks and adverse reactions and specific tests, observations and precautions that may be necessary for the clinical trial. This understanding should be based on available physical, chemical, pharmaceutical, pharmacological, toxicological and clinical information on the product(s) being tested. 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If a product placed on the market is being investigated for new uses (i.e. a new indication), an IB specific to this new use should be prepared. IB should be reviewed at least once a year and revised as necessary in accordance with the adjuthrator's written procedures. Depending on the stage of development and the production of relevant new information, a more frequent revision may be more appropriate. However, in accordance with good clinical practice, the relevant new information may be so important that it is communicated to the investigators and, where applicable, to the Institutional Review Committees (IEC)/Independent Ethics Committee (IEC) and/or regulatory authorities before it is included in the revised IB. The sponsor is generally responsible for ensuring that up-to-date IB is available to researchers and that investigators are responsible for providing up-to-date IB. In the case of a trial sponsored by a researcher, the sponsor-researcher should determine whether the brochure is available from a commercial manufacturer. If the test product is provided by a sponsor-researcher, then it should provide the necessary information to the test staff. In cases where the preparation of a formal IB is impractical, the investigator-examiner should provide as a substitute an extended part with supporting documents in the test report containing up-to-date information described in this Guideline. 7.2 IB's general considerations should include: 7.2.1 The name of the Site This should provide the name of the sponsor, the identity of each product under investigation (i.e. research number, chemical or approved generic name and trade name(s), if legally permissible and requested by the sponsor) and the date of issue. It is also proposed to provide an issue number and a reference to the number and date of issue it replaces. An example is given in Appendix 1. 7.2.2 Confidentiality Statement The sponsor may wish to include a statement ordering the examine/consignee to treat IB as a confidential document for exclusive information and use of the investigation team and the IRB/IEC. 7.3 The content of the IB investigative brochure should contain the following sections, each with literature references, if applicable: 7.3.1 Content The content example is given in Appendix 2 7.3.2 Summary A concise summary (preferably not exceeding two pages) should be provided highlighting the relevant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic and clinical information relevant to the clinical development stage of the investigational medicinal product. 7.3.3 Introduction A brief introductory statement should be provided containing the chemical name (and the common and trade name(s) if all active substances are approved, the pharmacological substance(s) of the investigational medicinal product(s) and its expected position in this class (e.g. benefits), the rationale for carrying out research on the products under investigation and the presumed prophylactic, therapeutic or diagnostic indication(s). Finally, the introductory statement should provide a general approach to be followed when assessing the product under investigation. 7.3.4 The physical, chemical and pharmaceutical properties and formula A should provide a description of the substances of the product under investigation (including the chemical and/or structural formula(s)) and a brief summary of the relevant physical, chemical and pharmaceutical properties should be provided. In order to allow for appropriate precautions to be taken during the experiment, a description of the formulation(s) to be used, including excipients, should be provided and justified where clinically relevant. Instructions for storing and handling dosing forms should also be provided. Any structural similarities with other known compounds should be reported. 7.3.5 Preclinical studies Introduction: The results of all relevant studies on non-clinical pharmacology, toxicology, pharmacokinetics and metabolism of the products under investigation should be provided in an aggregated form. This summary should address the methodology used, the results and the discussion of the relevance of the findings for the therapeutic and potential adverse and unintended effects on humans investigated. information provided may include, where appropriate: - Nature and frequency of pharmacological or toxic effects - Severity or intensity of pharmacological or toxic effects - Time to onset of effects - Reversibility of effects - Duration of effects - Dose response Test species Number and sex of animals in each group Unit dose (e.g. Milligram/kilogram (mg/kg)) Dosing interval Dosing route Duration of dosing Duration Of systemic distribution Duration of subsequent results after exposure Including the following aspects: Tabular format/lists should be used whenever possible to improve presentation clarity. The following sections should discuss the most important findings from studies, including the response of observed dose effects, relevance to humans and all aspects to be studied in humans. Where appropriate, effective and non-toxic dose findings in the same species should be compared (i.e. the therapeutic index should be discussed). The relevance of this information to the proposed human behavior should be addressed. Where possible, blood/tissue levels should be compared rather than mg/kg. (a) Preclinical pharmacology A summary of the pharmacological aspects of the products under investigation and, where appropriate, of its major metabolites studied in animals should be included. Such a summary should include studies assessing potential therapeutic activity (e.g. efficacy models, receptor binding and specificity) as well as safety assessment studies (e.g. specific studies to assess pharmacological measures other than the intended therapeutic effects). (b) Pharmacokinetics and metabolism of products in animals A summary of the pharmacokinetics and biological transformation and disposition of investigational medicinal products in all species studied should be provided. The discussion of the findings should address the absorption and local and systemic bioavailability of the products and metabolites studied and their relationship to pharmacological and toxicological findings in animal species. (c) Toxicology Summary of toxicological effects surveyed in relevant studies conducted in different species should be described, where appropriate, in the following headings: 7.3.6 Effects on humans Introduction: A thorough discussion should be provided on the known effects of investigational medicinal products in humans, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided concerning the results of any use of the products tested other than in clinical trials, such as experience during marketing. (a) Pharmacokinetics and metabolism of products in humans. (b) Safety and efficacy The summary of information should be the safety, pharmacodynamics, efficacy and dose response obtained from previous human studies (healthy volunteers and/or patients), as appropriate, the safety of investigational medicinal products/products (including metabolites where appropriate). The implications of this information should be discussed. In cases where several clinical trials have been completed, the use of safety and efficacy summaries in several trials as indicated in subgroups may provide a clear presentation of the data. Tabulation summaries of adverse drug reactions would be useful for all clinical studies (including those for all indications studied). Important differences in models/incidences of adverse drug reactions between indications or subgroups should be discussed. IB should provide a description of the potential risks and adverse reactions to the medicinal product to be expected from previous experience with the medicinal product under investigation and the related medicinal product. A description of the preventive measures or specific monitoring to be carried out as part of the examination of the use of the product(s) should also be provided. (c) Experience with the placing on the market of bib should identify the countries in which the product under investigation has been placed on the market or approved. All relevant information resulting from the use of the product after placing it on the market (e.g. formulations, doses, routes of administration and adverse drug reactions) should be summarised. IB should also identify all countries where the product under investigation has not received a marketing authorisation/registration or has been withdrawn from placing on the market/registration. 7.3.7 Summary of data and guidelines for the investigator This section should provide an overall debate on preclinical and clinical data and summarise information from different sources on the different aspects of the products tested where possible. In this way, investigators may be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, published reports on related products should be discussed. This could help the investigator anticipate adverse drug reactions or other problems in clinical trials. The overall objective of this section is to provide investigators with a clear understanding of the potential risks and adverse reactions and specific tests, observations and precautions that may be necessary for the clinical trial. This understanding should be based on available physical, chemical, pharmaceutical, pharmacological, toxicological and clinical information on the product(s) being tested. The clinical investigator should also be provided with guidance on the recognition and treatment of possible overdose and adverse drug reactions based on previous human experience and the pharmacology of the investigational medicinal product 7.4 APPENDIX 1: PAGE TITLE (Example) SPONSOR NAME Product: Research No: Name: Chemical, Generic (if approved) Name(s) (if legally admissible and requested by the sponsor) INVESTIGATOR's ISSUE NUMBER: Date of issue: Replaces previous issue Number: Date: 7.5 APPENDIX 2: CONTENTS OF THE INVESTIGATOR'S BROCHURE (Example) - Confidentiality statement (optional) ..... 1 Content ..... 2 Summary ..... 3 Introduction ..... 4 Physical, chemical and pharmaceutical properties and formulation ..... 5 Preclinical study ..... 5.1 Preclinical pharmacology ..... 5.2 Pharmacokinetics and metabolism of products in animals ..... 5.3 Toxicology ..... 6 Effects in humans ..... 6.1 Pharmacokinetics and metabolism of products in humans ..... 6.2 Safety and efficacy ..... 6.3 Marketing experience ..... 7 Summary of data and guidelines for the investigator ..... NB: References to 1. Publications 2. Messages These references should be found at the end of each chapter Supplements (if any) Single dose carcinogenicity In special studies (e.g. Irritability and sensitisation) Reproductive toxicity Genotoxicity (mutagenicity) A summary of information on the pharmacokinetics of the investigational medicinal product(s) should be submitted, including, where available: pharmacokinetics (including metabolism, where appropriate, and absorption, plasma protein binding, distribution and elimination). Bioavailability of the products under investigation (absolute, if possible and/or relative) using the reference dosing formulation. Population subgroups (e.g. gender, age and impaired organ function). interactions (e.g. drug-product interactions and food effects). Other pharmacokinetic data (e.g. results of population studies conducted in clinical trials). 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(a) Pharmacokinetics and metabolism of products in humans. (b) Safety and efficacy Summary of safety information of the investigational medicinal product(s) (including metabolites, where appropriate) safety, pharmacodynamics, efficacy and dose response obtained from previous human studies (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where several clinical trials have been completed, the use of safety and efficacy summaries in several trials as indicated in subgroups may provide a clear presentation of the data. Tabulation summaries of adverse drug reactions would be useful for all clinical studies (including those for all indications studied). Important differences in models/incidences of adverse drug reactions between indications or subgroups should be discussed. 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Guidance should also be provided to the clinical trial on the recognition and treatment of possible overdose and adverse drug reactions, based on previous human experience Pharmacology of the products under investigation 7.4 APPENDIX 1: COVER PAGE (Example) NAME OF SPONSOR Product: Research number: Name(s): Chemical, General (if approved) Business name (if legally permissible and required by the sponsor) Investigator's issue number: Date of issue: Replaces previous issue number: Date: 7.5 APPENDIX 2: CONTENTS OF THE INVESTIGATOR'S BROCHURE (Example) - Declaration of confidentiality (optional) ..... 1 Content ..... 2 Summary ..... 3 Introduction ..... 4 Physical, chemical and pharmaceutical properties and formulation ..... 5 Preclinical study ..... 5.1 Preclinical pharmacology ..... 5.2 Pharmacokinetics and metabolism of products in animals ..... 5.3 Toxicology ..... 6 Effects in humans ..... 6.1 Pharmacokinetics and metabolism of products in humans ..... 6.2 Safety and efficacy ..... 6.3 Marketing experience ..... 7 Summary of data and guidelines for the investigator ..... 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