1.0

Nationale Richtlinien

Einführung

Prüfrichtlinien für Humanarzneimittel

Arzneimittelprüfrichtlinien gemäß § 26 des Arzneimittelgesetzes (AMG) wurden erstmals im Jahr 1989 konzipiert. Sie hatten die Form einer Allgemeinen Verwaltungsvorschrift und sollten den Behörden als Anleitung dienen, nach der sie Anträge auf Verkehrsgenehmigungen für Humanarzneimittel zu beurteilen hatten. Die Allgemeine Verwaltungsvorschrift vom 14. Dezember 1989 (BAnz. Nr. 243 a) ist am 1. Januar 1990 in Kraft getreten. Mit ihr wurde die EG-Richtlinie 75/318/EWG (Europäische Prüfrichtlinie) vom 20. Mai 1975 (ABI. EG Nr. 147 S. 1 vom 9. Juni 1975) formell in nationales Recht transformiert.[1]

Mit der Allgemeinen Verwaltungsvorschrift zur Änderung der Allgemeinen Verwaltungsvorschrift zur Anwendung der Arzneimittelprüfrichtlinien vom 22. Dezember 1994 (BAnz. S. 12569) wurden die Prüfrichtlinien an den Stand der Wissenschaft angepasst. Dabei wurden Teile der Vorschriften über die analytische, pharmakologisch-toxikologische und klinische Prüfung durch die entsprechenden Abschnitte der europäischen Richtlinie 91/507/EWG vom 19. Juli 1991 (ABI. EG Nr. L 270 S. 32) ersetzt.[2] Zugleich wurde der Anwendungsbereich auf Sera, Impfstoffe und Testallergene ausgedehnt.

Durch die 2. Änderung der Allgemeinen Verwaltungsvorschrift vom 11. Oktober 2004 (BAnz. S. 22037) wurde die Richtlinie 2003/63/EG vom 25. Juni 2003 (ABI. EG L 159 S. 46) zur Änderung der Richtlinie 2001/83/EG zur Schaffung eines Gemeinschaftskodexes für Humanarzneimittel in nationales Recht transformiert. Durch diese Änderungsrichtlinie wurden einheitliche Anforderungen an das Zulassungsdossier festgelegt, die als Ergebnis der Internationalen Harmonisierungskonferenz (ICH) zu einem einheitlichen Gemeinsamen Technischen Dokument (Common Technical Dokument, CTD) führten. Für einzelne Arzneimittel wurden besondere Anforderungen festgelegt, so zum Beispiel eine Plasma-Stammdokumentation für aus Plasma gewonnene Arzneimittel, eine Impfantigen-Stammdokumentation, besondere Anforderungen für Gentherapeutika und Zelltherapeutika sowie für pflanzliche Arzneimittel.

In der Folge wurden die Anforderungen des Anhangs I der Richtlinie 2001/83/EG durch die Richtlinie 2009/120/EG der Kommission vom 14. September 2009 (ABl. L 242 vom 15.9.2009, S. 3) im Hinblick auf Arzneimittel für neuartige Therapien geändert. Die Änderung stand im Zusammenhang mit der Verordnung (EG) Nr. 1394/2007

1 K. Feiden. Pharm. Ind. 1990. S. 175
2 K. Feiden. Pharmarecht 1995. S. 150

vom 13. November 2007 über Arzneimittel für neuartige Therapien (ABl. L 324 vom 10.12.2007, S. 121). Danach wird eine Genehmigung für das Inverkehrbringen dieser Arzneimittel nur noch durch die Kommission im zentralen Zulassungsverfahren erteilt und nicht mehr durch die Bundesoberbehörden. Der Fünfte Abschnitt der Arzneimittelprüfrichtlinien („Arzneimittel für neuartige Therapien") wurde hierdurch gegenstandslos.

Prüfrichtlinien für Tierarzneimittel

Für Tierarzneimittel wurde die Allgemeine Verwaltungsvorschrift zur Anwendung der Tierarzneimittelprüfrichtlinien vom 30. März 1995 (BAnz. S. 4241) konzipiert. Sie wurde geändert durch Artikel 5 der Zweiten Allgemeinen Verwaltungsvorschrift zur Änderung der Allgemeinen Verwaltungsvorschrift zur Anwendung der Arzneimittelprüfrichtlinien vom 11. Oktober 2004 (BAnz. S. 22037). Diese nimmt Bezug auf die Richtlinie 2001/82/EG des Europäischen Parlaments und des Rates vom 6. November 2001 zur Schaffung eines Gemeinschaftskodexes für Tierarzneimittel (ABI. EG Nr. 311 S. 1).

Rechtsgrundlage umgestellt

Durch das Gesetz zur Änderung arzneimittelrechtlicher Vorschriften vom 15. April 2005 (BGBl. I S. 1068) wurde die Rechtsgrundlage für die Arzneimittelprüfrichtlinien gemäß § 26 Abs. 1 AMG in Angleichung an Formerfordernisse des Gemeinschaftsrechts von der bisherigen Rechtsform der Allgemeinen Verwaltungsvorschrift auf die Rechtsform der Verordnung umgestellt. Hiernach muss das für das Gesundheitswesen zuständige Bundesministerium die Anforderungen an die gemäß §§ 22 bis 24 AMG, auch in Verbindung mit § 38 Abs. 2 (Registrierung homöopathischer Arzneimittel) und § 39b Abs. 1 (Registrierung traditioneller pflanzlicher Arzneimittel) AMG, vorzulegenden Unterlagen durch Rechtsverordnung erlassen. Durch den Wegfall der Rechtsgrundlage für die allgemeinen Verwaltungsvorschriften bleiben die bestehenden Arzneimittelprüfrichtlinien weiterhin in Kraft. Die Aktualisierung muss jedoch in Form einer Rechtsverordnung erfolgen.

Gleitende Verweise auf die Prüfrichtlinien der EU

Die Überführung von der bisherigen Allgemeinen Verwaltungsvorschrift in eine Rechtsverordnung wurde für die Tierarzneimittel-Prüfrichtlinien mit der Tierarzneimittel-Prüfrichtlinienverordnung (TamPV) vom 18. Februar 2010 (BGBl. I S. 130) und für Humanarzneimittel mit der Arzneimittelprüfrichtlinien-Verordnung (AMPV) vom 8. Januar 2016 (BGBl. I S. 47) vorgenommen. Die Anpassung der Arzneimittelprüfrichtlinien für Human- und für Tierarzneimittel geschieht durch eine gleitende Verweisung auf den Anhang I Teil I bis III der Richtlinie 2001/83/EG (Humanarzneimittel) bzw. Anhang I Titel I, II, III und IV Nummer 2 der Richtlinie 2001/82/EG (Tierarzneimittel) in der jeweils geltenden Fassung. Hierdurch wird sichergestellt, dass die jeweils auf Gemeinschaftsebene an den gesicherten Stand der wissenschaftlichen Erkenntnisse angepassten harmonisierten Anforderungen ohne Verzug in nationales Recht umgesetzt werden.

Adressat der Arzneimittelprüfrichtlinien

Die Arzneimittelprüfrichtlinien sind an die zuständigen Zulassungsbehörden gerichtet. Sie enthalten die Maßstäbe, die an die Zulassungsunterlagen zu stellen sind. Die Entscheidungskriterien über die Zulassung bzw. die Registrierung eines Arzneimittels

1.190 Arbeitskreis Blut: Bewertungen von Krankheitserregern, die durch Blut übertragen werden (Aufstellung über alle Stellungnahmen)

Der Arbeitskreis Blut des Bundesministeriums für Gesundheit und Soziale Sicherung gibt als nationales Beratungsgremium Stellungnahmen zu neuartigen Erregern ab, bewertet neue Erkenntnisse zu bekannten Erregern und erarbeitet entsprechende Empfehlungen für die Fachöffentlichkeit. Diese Serie von Stellungnahmen zu einzelnen Erregern wird als Zusammenfassung des aktuellen Wissensstandes im Bundesgesundheitsblatt veröffentlicht.

In der folgenden Aufstellung sind sämtliche zwischen 1998 und April 2016 vom Arbeitskreis Blut veröffentlichten Stellungnahmen enthalten. Sie wurden bis zum Jahr 2009 mit in die Arzneimittelprüfrichtlinien aufgenommen. Seitdem wird die Serie in diesem Kompendium nicht mehr weiter aktualisiert. Die bislang enthalten Dokumente werden aus dem Arzneimittelprüfrichtlinien herausgenommen, sofern sie durch Revision überholt sind.

Die Aufstellung der Stellungnahmen wird aus Gründen der Transparenz jedoch weiter fortgeführt.

Erreger	**Erscheinungsdatum**	**Bundesgesundheitsblatt, abgedruckt in**
Parvovirus B19	9. Februar 1998 Rev.: 7. September 2010	2/1998: 83–87 9/2010: 944–956
Creutzfeldt-Jakob-Erkrankung (CJK) bzw. humane übertragbare (transmissible) spongiforme Enzephalopathien (TSE)	9. Februar 1998	2/1998: 78–83
GB-Virus Typ C (GBV-C) (Hepatitis-G-Virus HGV)	9. Februar 1998	2/1998: 88–90
Humane T-Zell lymphotrope Viren Typ 1 und 2 (HTLV-I/-II)	10. November 1998	11/1998: 512–517 Kap. 1.191
Yersinia enterocolitica	13. Juli 1999	7/1999: 613–621 Kap. 1.195

Erreger	**Erscheinungsdatum**	**Bundesgesundheitsblatt, abgedruckt in**
Humanes Cytomegalovirus (HCMV)	8. August 2000 Rev.: 7. September 2010	8/2000: 653–659 9/2010: 973–983
TT-Virus	8. Februar 2000	2/2000: 154–156 Kap. 1.196
Hepatitis B Virus (HBV)	14. März 2000	3/2000: 240–248 Kap. 1.197
Hepatitis A Virus (HAV)	14. August 2001	8/2001: 844–850
Treponema pallidum	8. Oktober 2002	10/2002: 818–826
Hepatitis-C-Virus (HCV)	12. August 2003	8/2003: 712–722 Kap. 1.199a
Arboviren – durch Arthropoden übertragbare Viren	14. September 2004	9/2004: 910–918 Kap. 1.200
Coxiella burnetii – Erreger des Q (query) Fiebers	12. Juli 2005 Rev.: 18. Juli 2013	7/2005: 814–821 8/2013: 1178–1190
Variante Creutzfeldt-Jakob-Krankheit	13. September 2005	9/2005: 1082–1090 Kap. 1.203
Influenzaviren	9. September 2007	9/2007: 1184–1191 Kap. 1.205
Arbobakterien (über Arthropoden übertragbare Bakterien)	9. September 2007	9/2007: 1192–1207 Kap. 1.206
Hepatitis-E-Virus	8. Januar 2008 Rev.: 8. Oktober 2014	1/2008: 90–97 2/2015: 198–218
Malaria	2. Februar 2008	2/2008: 236–249 Kap. 1.208
Arboprotozoen	3. Februar 2009	2/2009: 123–146 Kap. 1.209
Orthopockenviren: Infektionen des Menschen	7. September 2010	9/2010: 957–972
Dengue Fieber Virus (DENV)	4. Juli 2011	7/2011: 892–904

2.60

Non-Clinical Local Tolerance Testing of Medicinal Products*

October 2015

Table of Content

* Doc. Ref. EMA/CHMP/SWP/2145/2000 Rev. 1, Corr. 1 – References update
This Guideline replaces 'Note for Guidance on Non-Clinical Local Tolerance Testing of Medicinal Products' (CPMP/SWP/2145/00).

Executive Summary

This document provides guidance for the development and evaluation of medicinal products that will, or have the potential to, come into contact with different sites of the human body following normal clinical use, as well as after unintentional administration. In order to reduce the number of animals as much as possible, local tolerance testing should, whenever possible, be part of other toxicity studies, and efforts should be made to include appropriate endpoints. "Stand-alone" studies on local tolerance are generally not recommended. Separate studies on excipients with prior clinical safety data are generally not required.

1. Introduction (Background)

Non-clinical local tolerance testing is intended to support human exposure to a drug product (both active substance and excipients) at contact sites of the body following clinical use. Such local tolerance testing should aim to support initial testing in clinical trials, as well as intending to support the final product. The non-clinical study design should aim to distinguish between any physical consequences of administration, e.g. local trauma following injection, or purely physico-chemical actions of the product from local toxicological or pharmacodynamic effects. Separate studies on excipients with prior clinical safety data are generally not required.

In accordance with Directive 2010/63/EU on the Protection of Animals Used for Scientific Purposes, a scientifically satisfactory method or testing strategy, not entailing the use of live animals should be used wherever possible. Where no alternative method is recognised by the legislation of the Union, the numbers of animals used may be reduced by resorting to other methods and by implementing testing strategies that would replace, reduce and refine the use of animals. The Guideline on regulatory acceptance of 3R testing approaches should be consulted before conducting non-clinical studies.

It is recommended that if animal studies are necessary for an evaluation of local tolerance by the intended clinical route of administration, such an evaluation is included as part of the general toxicity studies whenever possible, and not as a "stand-alone" study.

2. Scope

This document provides guidance on the non-clinical local tolerance testing to support the clinical development and marketing authorisation of medicinal products for human use. Studies on impurities arising from the active substances or excipients present in the drug product or extracted or leached from a container closure system are not directly covered by this guideline.

The principles outlined in this guidance should be applicable to all types of drug products, including biotechnology-derived pharmaceuticals and herbal products. However, for biotechnology-derived pharmaceuticals reference should also be made to the ICH S6(R1) guideline.

2.106a

Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders*

June 2016

Table of Contents

* Doc. Ref. EMA/CHMP/748108/2013, Rev. 3
This Guideline replaces the 'Guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013)'. The changes follow the adoption of the CHMP 'Reflection paper (RP) on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015)' and were are aligned with simultaneously adopted modifications to the CHMP 'Guideline on Clinical investigation on medicinal products in the treatment of hypertension (EMA/CHMP/29947/2013/Rev. 4)' and the 'CHMP Guideline on clinical evaluation of medicinal products used in weight management (EMA/CHMP/311805/2014)'. Hence the CHMP considered that the Concept Paper and the public consultation phases are not needed as they took place in the context of implementation of the RP where already reference is made to this guideline. This justification is provided in line with the 'Procedure for European Union Guidelines and Related documents within the pharmaceutical legislative framework (EMEA/P/24143/2004 Rev. 1 corr)'.

Executive Summary

This document is the revised version of the 'Note for guidance on clinical investigation of medicinal products in the treatment of lipid disorders (CHMP/EWP/3020/03)'. It is intended to provide guidance for the evaluation of drugs in the treatment of lipid disorders and details the main regulatory requirements that are expected to be followed in the development of a lipid modifying medicinal product. In particular, the sections concerning the recommended endpoints and long term safety data, including morbidity and mortality data, have been updated. Furthermore the document was updated following finalisation of the *Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015)*. Latterly, there is an attempt to use imaging modalities as surrogate markers of outcome benefit with lipid modifying agents in many trials. This section of the guideline has also been revised in order to provide a discussion of regulatory aspects of these markers.

1. Introduction (Background)

Lipid disorders may manifest in different ways, leading to changes in plasma lipoproteins levels and/or function. Lipid disorders are commonly classified according to the prevailing laboratory abnormality, but this classification does not accurately represent the different genetic and metabolic defects, or clinical syndromes. Blood lipid levels may be affected by other clinical conditions such as diabetes mellitus, thyroid disorders or nephrotic syndrome; in such cases, the lipid levels should be reassessed once the underlying disease has been controlled or treated.

Lipid disorders most often imply hypercholesterolemia. A large body of epidemiological evidence now exists demonstrating a strong positive correlation and causal relationship between serum low density lipoprotein cholesterol (LDL-C), and the risk of coronary heart disease (CHD). Other clinical manifestations of atherosclerosis also appear linked to plasma LDL-C levels such as cerebrovascular disease (i.e. stroke) or peripheral vascular disease. In addition, clinical trials have shown that LDLlowering therapy with HMG-Co A reductase inhibitors reduces risk for CHD. The relationship between LDL-C levels and CHD risk is present over a broad range of LDL levels. The dividing line between „normocholesterolemia" and „hypercholesterolemia" is arbitrary and in fact may be non-existent.

Epidemiologic data indicate a continuous increasing risk from very low to "normal" and high levels of LDL-C.

Treatment decisions are based not only on the level of LDL-C, but on the overall, multifactorial level of cardiovascular risk. Modifications of LDL-C goals are discerned on the basis of:

- Presence of clinical forms of atherosclerosis (CHD, ischemic stroke or peripheral vascular disease)
- Diabetes mellitus
- Chronic kidney disease
- Integrated global risk scoring models (e.g. SCORE)
- Monogenic dyslipidaemia (e.g. familial hypercholesterolemia)

Concomitantly other lipid disorders may be present, in particular hypertriglyceridemia ("mixed hyperlipidemia"). In addition, lipid disorders may also implicate isolated or prevalent hypertriglyceridemia and/or low high density lipoprotein cholesterol (HDL-C). Although elevated triglycerides (TG) are noted as a risk factor, the evidence on the benefits of lowering elevated TG levels is still modest when LDL-C and HDL-C changes are corrected for. The treatment strategy for elevated TG depends on the causes of the elevation and its severity. Low HDL -C level, whether or not in conjunction with elevated LDL-C or TG levels, has also been shown to be a risk factor for cardiovascular disease (CVD). Low HDL-C warrants clinical attention although the goal of therapy needs further specification due to lack of direct evidence that raising HDL-C is associated with CVD prevention. More recently other lipoproteins e.g. lipoprotein Lp(a) and apolipoprotein Apo(B), have also been investigated as possible risk factors for CHD. However, their role is not clearly defined at the present time.

2. Scope

The guideline provides advice to applicants on the main regulatory requirements that are expected to be followed in the development of a medicinal product for treatment of lipid disorders associated with increased cardiovascular risk encountered in adult patients (i.e. lipid modifying agents). Lipid disorders in paediatric patients are addressed in a separate addendum.

3. Legal Basis and Relevant Guidelines

This guideline should be read in conjunction with the introduction and general principles and Annex I to Directive 2001/83 as amended and with the following guidelines:

- Note for Guidance on General Considerations for Clinical Trials (CHMP/ICH/291/95, ICH E8[1])
- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95, ICH E6)
- Note for Guidance on Dose Response Information to support Drug Registration (CPMP/ICH/378/95, ICH E4)
- Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96, ICH E9)
- Note for Guidance on Choice of Control Group for Clinical Trials (CPMP/ICH/364/96, ICH E10)
- Guideline on the choice of the Non-inferiority margin (EMEA/CPMP/EWP/2158/99)
- Points to Consider on Switching between Superiority and Non-inferiority (CPMP/EWP/482/99)
- Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95)
- Note for Guidance on Population Exposure: The extent of population exposure to assess clinical safety (CPMP/ICH/375/95 adopted November 1994)
- ICH E7: Studies in support of special populations: geriatrics

1 Für die Fundstellen zu den Kap. in diesem Werk siehe Register III und IV.

2.769a Substances Considered as not Falling within the Scope of Regulation (EC) No. 470/2009*, with Regard to Residues of Veterinary Medicinal Products in Foodstuffs of Animal Origin**

April 2016

1. Background Information

Regulation (EC) No. 470/2009 of 6 May 2009 lays down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin. The Regulation repealed Council Regulation (EEC) No. 2377/90.

Article 1(a) of Regulation (EC) No. 470/2009 defines its scope as follows:

"For the purposes of ensuring food safety, this Regulation lays down rules and procedures in order to establish:

a) the maximum concentration of a residue of a pharmacologically active substance which may be permitted in food of animal origin (maximum residue limit);

(…)"

Article 1(3) of the Regulation states that:

> "This Regulation shall not apply to ‚active principles of biological origin intended to produce active or passive immunity or to diagnose a state of immunity, used in immunological veterinary medicinal products'."

In Article 2(a) it is specified that "residues of pharmacologically actives substances" means all pharmacologically active substances, expressed in mg/kg or µg/kg on a fresh weight basis, whether active substances, excipients or degradation products, and their metabolites which remain in food obtained from animals.

Previously, in the context of the evaluation of MRL applications under Council Regulation (EC) No. 2377/90, the CVMP discussed the concept of "pharmacologically active substances", in particular considering the need for MRL evaluations for excipients and manufacturing materials. As detailed in the CVMP publication entitled *Position Paper on the definition of substances capable of pharmacological action in the context of Directive 2001/82/EC, as amended, with a particular reference to excipientsand manufacturing materials* (EMEA/

* Regulation (EC) No. 470/2009 of the European Parliament and of the Council of 6 May 2009, repealing Council Regulation (EEC) No. 2377/90

** Doc. Ref. EMA/CVMP/519714/2009–Rev.34

CVMP/072/97-Rev.1[1]), it was concluded that "*substances capable of pharmacological action are substances pharmacodynamically active at the dose at which they are administered to the target animal by means of the veterinary medicinal product in which they are included"*. It follows that if an excipient has not pharmacodynamically activity at the relevant dose, then no MRL evaluation would be needed.

Subsequently, the Committee adopted a paper entitled *Reflection Paper on consideration of adjuvants and preservatives under Council Regulation (EEC) No. 2377/90 laying down a community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin* (EMEA/CVMP/339116/2007 – Consultation), in which it is concluded that the approach used to determine whether an MRL evaluation is required for preservatives and adjuvants should be the same as is used in relation to excipients (i.e. it should be based on the presence or absence of pharmacodynamic activity at the intended dose).

Since the implementation of Council Regulation (EEC) No. 2377/90, the CVMP has deliberated on many substances (including excipients, adjuvants and preservatives) to be used in veterinary medicinal products intended for food producing species, and regularly receives requests (either scientific advice or ad hoc requests) to consider whether such substances fall within the scope of the MRL regulation.

The substances for which the CVMP has concluded that no MRL evaluation is required are listed in the CVMP publication "Substances considered as not falling within the scope of Regulation (EEC) No. 2377/90" (EMEA/CVMP/046-00), also often referred to as the 'out of scope list'.

The list also includes a small number of compounds that do not fall within the categories of excipients, adjuvants or preservatives but are natural substances essential for life or are biologically active constituents. Due to the nature of these specific compounds the CVMP considered that an evaluation for the establishment of maximum residue limits would not be appropriate.

Following the implementation of Regulation (EC) No. 470/2009 there was a need to update the background information and legal references included in the document containing the 'out of scope list'. This document performs that function and supersedes the CVMP publication *Substances considered as not falling within the scope of Council Regulation (EEC) No. 2377/90*. The list presented on the following pages includes all the substances included in the superseded document.

It should be noted that this list of substances is in no way exhaustive and includes only substances for which requests in this respect were made to CVMP by a company or a national authority.

Any enquiries may be sent to mrl@ema.europa.eu

1 Initially adopted in April 1997 and further revised in July 2004

2.2003

European Union Herbal Monograph on *Linum usitatissimum* L., Semen*

March 2015

1. Name of the Medicinal Product

To be specified for the individual finished product.

2. Qualitative and Quantitative Composition[1, 2]

Well-established use	***Traditional use***
With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC as amended	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC as amended
Linum usitatissimum L., semen (linseed)	*Linum usitatissimum* L., semen (linseed)
i) Herbal substance As defined in the Ph. Eur. monograph	i) Herbal substance As defined in the Ph. Eur. monograph
ii) Herbal preparations not applicable	ii) Herbal preparations not applicable

3. Pharmaceutical Form

Well-established use	***Traditional use***
Herbal substance for oral use.	Herbal substance for oral use.
The pharmaceutical form should be described by the European Pharmacopoeia full standard term.	The pharmaceutical form should be described by the European Pharmacopoeia full standard term.

* Doc. Ref. EMA/HMPC/377675/2014

1 The declaration of the active substance(s) for an individual finished product should be in accordance with relevant herbal quality guidance.

2 The material complies with the Ph. Eur. monograph (ref.: 0095).

4. Clinical Particulars

4.1 Therapeutic Indications

Well-established use	*Traditional use*
Herbal medicinal product for the treatment of habitual constipation or in conditions in which easy defaecation with soft stool is desirable.	Traditional herbal medicinal product used as a demulcent preparation for the symptomatic relief of mild gastrointestinal discomfort. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.

4.2 Posology and Method of Administration

Well-established use	*Traditional use*
Posology *Adolescents, adults and elderly* Single dose 10–15 g, Daily dose: 2–3 times daily The use in children under 12 years of age is not recommended (see section 4.4 'Special warnings and precautions for use'). **Duration of use** If the constipation does not resolve within 3 days, a doctor or a pharmacist should be consulted. **Method of administration** Oral use. Take 10–15 g seeds with 150 ml water, milk, fruit juice or similar aqueous liquid 2–3 times daily; then maintain adequate fluid intake. The product should be taken during the day at least ½ to 1 hour before or after intake of other medicines. The effect starts 12–24 hours later. Warning: not to be taken immediately prior to bedtime.	**Posology** *Adolescents, adults and elderly* Single dose 5–10 g in 250 ml water Daily dose: up to three times during the day The use in children under 12 years of age is not recommended (see section 4.4 'Special warnings and precautions for use'). **Duration of use** If the symptoms persist for longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. **Method of administration** Oral use. For a mucilaginous preparation, soak 5–10 g whole or broken seeds in 250 ml water for at least <x min> and take this half an hour before eating. At the time of consumption the process of swelling has to be accomplished [length has to be specified for the individual product]. The mucilaginous preparations may be consumed with or without the seeds.

4.20 EU Official Control Authority Batch Release for Human Biological Medicines – Overview of Products Specific Guidelines*

February 2017

Document Title	Last Web Update	In Force from
User Guidannce		
Preface and Notes for Use	01/08/14	x
Explanatory Note on Correct Application of Section 3.2 of Product Specific Guidelines for Official Control Authority Batch Release	30/06/15	01/08/15
OCABR Administrative Procedures		
EU Administrative Procedure for Official Control Authority Batch Release	17/08/16	01/09/16
Procedure for Official Control Authority Batch Release of Centrally Authorised Immunological Medicinal Products for Human Use and Medicinal Products Derived From Human Blood and Plasma	01/08/14	01/07/10
Medicinal Products Derived From Human Blood and Human Plasma – Product Specific Guidelines		
Clotting Factor Concentrates, Plasma Inhibitor Concentrates and Fibrin Sealants	19/05/16	15/06/16
Human Albumin	01/08/14	01/01/12
Human Immunoglobulin	17/08/16	01/09/16
Human Plasma (pooled and treated for virus inactivation) formerly Solvent-Detergent (SD) Plasma	25/11/14	01/01/15
Protocol for Approval of Plasma Pools	25/11/14	01/01/15

* www.edqm.eu, Stand: 05.02.2017

Document Title	Last Web Update	In Force from
Immunological Products Consisting of Vaccines – Product Specific Guidelines		
BCG Vaccine	01/08/14	01/01/12
Cell Cultured Influenza Vaccine (Surface Antigen, inactivated)	01/08/14	01/01/12
Cholera Vaccine (Oral, inactivated)	01/08/14	01/01/12
Diphtheria and Tetanus Vaccine (adsorbed)	01/08/14	01/01/12
Diphtheria, Tetanus and Hepatitis B (rDNA) Combined Vaccine (adsorbed)	01/08/14	01/01/12
Diphtheria, Tetanus and Pertussis (Acellular Component) Combined Vaccine (adsorbed)	12/12/14	01/02/15
Diphtheria, Tetanus and Pertussis (Whole Cell) Combined-Vaccine (adsorbed)	01/08/14	01/01/12
Diphtheria, Tetanus and Poliomyelitis (inactivated) Combined Vaccine (adsorbed)	01/08/14	01/01/12
Diphtheria, Tetanus, Pertussis (Acellular Component) with separate Haemophilus Type B Conjugate Combined Vaccine (adsorbed)	08/03/16	01/04/16
Diphtheria, Tetanus, Pertussis (Acellular Component) and Hepatitis B (rDNA) Combined Vaccine (adsorbed)	01/08/14	01/01/13
Diphtheria, Tetanus, Pertussis (Acellular Component), Poliomyelitis (inactivated) and Haemophilus Type B Conjugate Liquid Combined Vaccine	08/03/16	01/04/16
Diphtheria, Tetanus, Pertussis (Acellular Component), Poliomyelitis (inactivated) with separate Haemophilus Type B Conjugate Combined Vaccine (adsorbed)	08/03/16	01/04/16
Diphtheria, Tetanus, Pertussis (Acellular Component), Poliomyelitis (inactivated) Combined Vaccine (adsorbed)	01/08/14	01/01/13
Diphtheria, Tetanus, Pertussis (Acellular Component), Poliomyelitis (inactivated), Hepatitis B (rDNA) and Haemophilus Type B Conjugate Combined Vaccine (adsorbed)	12/07/16	25/07/16
Diphtheria, Tetanus, Pertussis (Acellular Component), Poliomyelitis (inactivated), Hepatitis B (rDNA) with separate Haemophilus Type B Conjugate, Combined Vaccine (adsorbed)	08/03/16	01/04/16
Diphtheria, Tetanus, Pertussis (Whole Cell) and Poliomyelitis (inactivated) Combined Vaccine (adsorbed)	01/08/14	01/01/12

6.0 Organization for Economic Cooperation and Development (OECD) – Einführung

Das Übereinkommen über die wirtschaftliche Zusammenarbeit und Entwicklung (OECD) wurde im Jahr 1960 geschlossen. Ziele sind die Förderung der wissenschaftlichen, technischen und wirtschaftlichen Entwicklung der Vertragsstaaten und die Ausweitung des Welthandels.

Der OECD gehören folgende 35 Vertragsstaaten an: Australien, Belgien, Chile, Deutschland, Dänemark, Estland, Finnland, Frankreich, Griechenland, Irland, Island, Israel, Italien, Japan, Kanada, Korea, Lettland, Luxemburg, Mexiko, Neuseeland, Niederlande, Norwegen, Österreich, Polen, Portugal, Schweden, Schweiz, Slowakei, Slowenien, Tschechien, Türkei, Spanien, Ungarn, USA, Vereinigtes Königreich.

Die Organisation kann verbindliche Beschlüsse fassen, Empfehlungen an die Vertragsstaaten richten und Vereinbarungen treffen. Die Grundsätze zur Guten Laborpraxis sind Empfehlungen, die von den Vertragsstaaten im Interesse der gegenseitigen Anerkennung der Sicherheitsprüfungen in nationales Recht transformiert werden müssen.

Die Europäischen Gemeinschaften haben die Anwendung der GLP-Grundsätze der OECD, die auf den Anhang 2 des Beschlusses des OECD Rates vom 12. Mai 1981 zurückgehen, mit den Richtlinien 87/18/EWG, 88/320/EWG und 90/18/EWG verbindlich gemacht. In Deutschland wurden sie durch die Aufnahme als Anhang 1 zu § 19a Abs. 1 des Chemikaliengesetzes umgesetzt.

Die GLP-Grundsätze der OECD wurden inzwischen weiterentwickelt und die Neufassung für die Mitgliedstaaten der Europäischen Union durch die Richtlinie 1999/11/EG (kodifiziert als Directive 2004/10/EC, abgedruckt unter Kap. 6.40) verbindlich gemacht. Die Neufassung wird durch Rechtsverordnung auf Grund des § 19d Abs. 2 des Chemikaliengesetzes (s. Kloesel/Cyran unter B 3.13) in nationales Recht transformiert. Kann der Nachweis über die Einhaltung der GLP-Grundsätze nicht erbracht werden, gelten die Prüfergebnisse nach § 19a Abs. 2 letzter Satz als nicht vorgelegt.

Die OECD Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring umfasst folgende Dokumente:

No.	Titel	Stand/ revised	Kapitel
OECD Principles of GLP			
Nr. 1	OECD-Grundsätze der Guten Laborpraxis	1997	6.1
GLP Consensus Documents			
Nr. 4	Qualitätssicherung und GLP	1999	6.42
Nr. 5	Einhaltung der GLP-Grundsätze durch Lieferanten	1999	6.43
Nr. 6	Die Anwendung der GLP-Grundsätze auf Freilandprüfungen	1999	6.44
Nr. 7	Die Anwendung der GLP-Grundsätze auf Kurzzeit-Prüfungen	1999	6.45
Nr. 8	Die Rolle und Verantwortlichkeiten des Prüfleiters bei GLP-Prüfungen	1999	6.46
Nr.10	GLP-Konsensdokument – Die Anwendung der GLP-Grundsätze auf Computergestützte Systeme, abgelöst durch Consensus Document Nr. 17	1995	–
Nr. 13	Die Anwendung der OECD GLP-Grundsätze auf Organisation und Management von Multi-site-Prüfungen	2002	6.48
Guidance Documents for Compliance Monitoring Authorities			
Nr. 2	Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice	1995	6.30
Nr. 3	Revised Guidance for the Conduct of Laboratory Inspections and Study Audit	1995	6.20
Nr. 9	Guidance for the Preparation of GLP Inspection Reports	1995	–
Advisory Documents of the Working Group on GLP			
Nr. 11	The Role and Responsibility of the Sponsor in the Application of the Principles of GLP	1998	6.47
Nr. 12	Requesting and Carrying Out Inspections and Study Audits in Another Country	2002	–
Nr. 14	Die Anwendung der OECD GLP-Grundsätze auf in vitro Prüfungen	2004	6.49
Nr. 15	Einrichtung und Betrieb von Archiven in Übereinstimmung mit den Grundsätzen der Guten Laborpraxis	2007	6.50

7.2 WHO Recommendations, Guidelines and other Documents Related to the Manufacture and Quality Control of Biological Substances used in Medicine Overview*

Recommendations, Guidelines and other documents	**Reference**
Adventitious agents, regulatory risk evaluation on finding an adventitious agent in a marketed vaccine: scientific principles	Adopted 2014, TRS 993 (2015)
Animal cells, use of, as in vitro substrates for the production of biologicals	Revised 2010, TRS 978 (2013)
BCG vaccines (dried)	Revised 2011, TRS 979 (2013)
Biological products: good manufacturing practices	Revised 2015, TRS 999 (2016)
Biological standardization and control: a scientific review commissioned by the UK National Biological Standards Board (1997)	Unpublished document WHO/BLG/97.1
Biological substances: International Standards and Reference Reagents	Revised 2004, TRS 932 (2006)
Biotherapeutic protein products prepared by recombinant DNA technology	Revised 2013, TRS 987 (2014)
Biotherapeutic products, similar	Adopted 2009, TRS 977 (2013)
Blood, blood components and plasma derivatives: collection, processing and quality control	Revised 1992, TRS 840 (1994)
Blood establishments: good manufacturing practices	Adopted 2010, TRS 961 (2011)
Blood plasma (human) for fractionation	Adopted 2005, TRS 941 (2007)
Blood plasma products (human): viral inactivation and removal procedures	Adopted 2001, TRS 924 (2004)
Blood regulatory systems, assessment criteria for national	Adopted 2011, TRS 979 (2013)

* WHO Expert Committee on Biological Standardization. Sixty-sixth report. WHO Technical Report Series 999, 2016.

IV. Register CHMP/ICH / CPMP/ICH Guidelines nach Codes

Dokument		Kapitel
CHMP/ICH/2/04		2.228
CHMP/ICH/423/02		2.229
CHMP/ICH/82260/2006		2.225
CHMP/ICH/83812/2013		2.232a
CHMP/ICH/126642/08		2.230
CHMP/ICH/126642/08		2.231
CHMP/ICH/167068/04		2.221
CHMP/ICH/353369/2013		2.224a
CHMP/ICH/380636/09		2.1310
CHMP/ICH/437986/06		2.1300
CHMP/ICH/518819/07	Annex	2.221a
CHMP/ICH/646107/08		2.220a
CHMP/ICH/731268/98		2.233
CHMP/ICH/772211/2012		2.231b
CPMP/ICH/135/1995		2.213
CPMP/ICH/136/95		2.203a
CPMP/ICH/137/95		2.214
CPMP/ICH/138/95		2.202a
CPMP/ICH/139/95		2.235
CPMP/ICH/140/95		2.210a
CPMP/ICH/141/95	neu: CHMP/ICH/126642/08	2.230
CPMP/ICH/174/95	neu: CHMP/ICH/126642/08	2.231
CPMP/ICH/279/95		2.227
CPMP/ICH/280/95		2.202b
CPMP/ICH/281/95		2.205a
CPMP/ICH/282/95, Rev.		2.224
CPMP/ICH/283/95	neu: CHMP/ICH/82260/2006	2.225
CPMP/ICH/286/96, Rev. 1		2.232
CPMP/ICH/288/95	+ Addendum (2003)	2.211a
CPMP/ICH/289/95		2.217
CPMP/ICH/291/95		2.215
CPMP/ICH/294/95		2.234
CPMP/ICH/295/95		2.236

VII. Register CVMP/VICH Guidelines nach Codes

Dokument	Nummer der Guideline	Kapitel
CVMP/VICH/095/01	GL25	2.859a
CVMP/VICH/096/01	GL 26	2.859b
CVMP/VICH/463/2002	GL 34	2.859c
CVMP/VICH/467/03 corr	GL 36 (R)	2.870
CVMP/VICH/468/03	GL 37	2.871
CVMP/VICH/484/02	GL 31	2.876
CVMP/VICH/485/02	GL 32	2.877
CVMP/VICH/486/02, Rev. 2	GL 33	2.873
CVMP/VICH/501/99	GL 17	2.860
CVMP/VICH/502/99, Rev. 1		2.225a
CVMP/VICH/525/00	GL 22	2.874
CVMP/VICH/526/2000	GL 23	2.875
CVMP/VICH/545/00	GL 20	2.849
CVMP/VICH/546/00	GL 21	2.850
CVMP/VICH/592/98	GL 6	2.890
CVMP/VICH/595/98	GL 9	2.880
CVMP/VICH/644/01	GL 27	2.872
CVMP/VICH/645/01, Rev. 1	GL 28	2.878
CVMP/VICH/790/03	GL 38	2.764
CVMP/VICH/810/04 corr.	GL 39	2.881
CVMP/VICH/811/04 corr.	GL 40	2.882
CVMP/VICH/833/99	GL 15	2.846
CVMP/VICH/834/99	GL 16	2.847
CVMP/VICH/835/99	GL 19	2.848
CVMP/VICH/837/99, Rev. 1	GL 10	2.857
CVMP/VICH/838/99, Rev. 1	GL 11	2.858
CVMP/VICH/899/99, Rev. 1	GL 3	2.861
CVMP/VICH/900/99	GL 4	2.862
CVMP/VICH/901/00	GL 5	2.863
CVMP/VICH/1052/04	GL 41	2.883
CVMP/VICH/359665/2005	GL 44	2.885
CVMP/VICH/393388/2006	GL 43	2.884
CVMP/VICH/463072/09	GL 46	2.873a
CVMP/VICH/463104/09	GL 47	2.873b