Marketing Authorisation Assessments

How do we carry out this function at the Medicines Authority?

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Introduction

This presentation is first and foremost a:

1. Sales pitch for scientists to join the Medicines Authority
2. Meant to shed light on how at the Medicines Authority we assess Marketing Authorisation applications
3. Present you with a different way at looking at Medicinal products

For a product to be placed on the Maltese market an applicant needs to submit a Marketing Authorisation Application to the Medicines Authority.

The Marketing Authorisation Application contains all the Documentation required to prove that a medicinal product is of Good Quality/ Efficacy/ Safe to be placed on the market.

According to Directive 2001/83/EC

- A Marketing Authorisation application submitted through the Centralised/ Decentralised procedures takes 210 Days.
- This time period excludes any clock stops during the procedure.
- Applicants submit responses to LOQs raised by Regulatory agencies involved in the procedure.

So what happens once a Marketing Authorisation Assessment is lodged with the Medicines Authority?

1. Date stamped

2. Validation

3. Assessment process- Step I
   Day 0 → Day 105

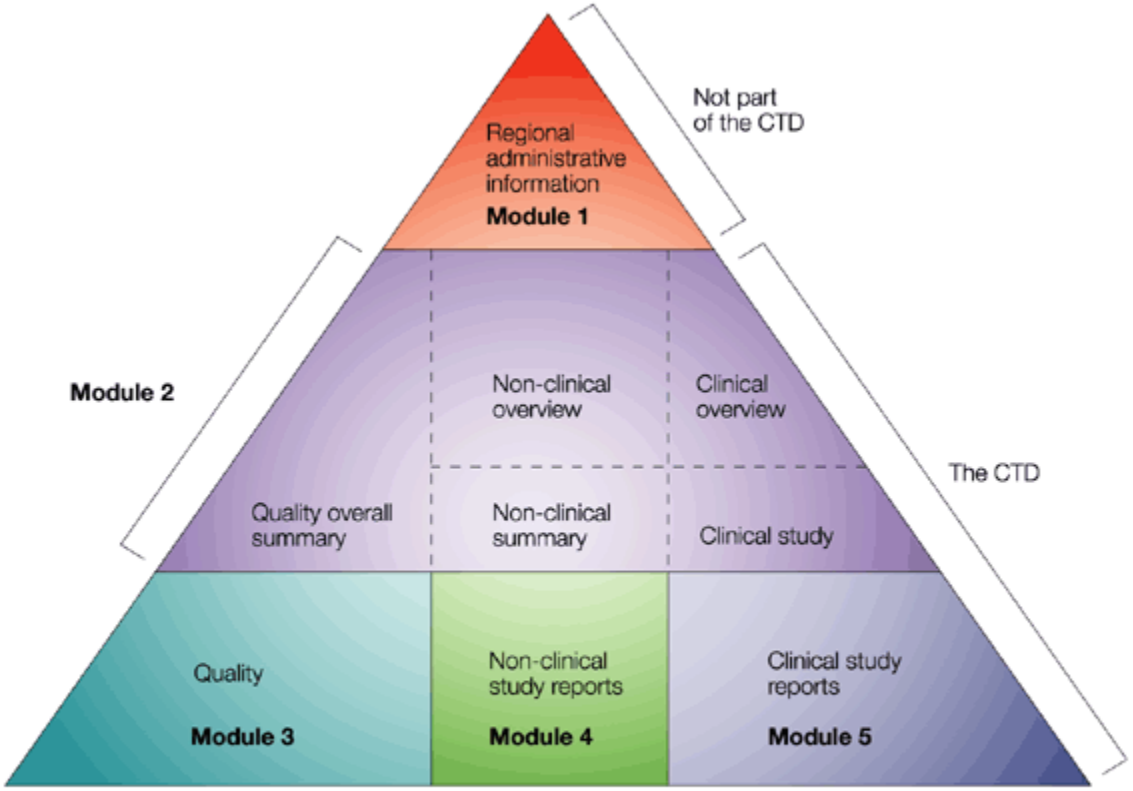
4. Assessment- Step II
   Day 106 → Day 210

5. Issue MA. Only if positive benefit-risk (B/R)

Therefore assessment of a Marketing Authorisation assessment is based on a B/R assessment of the Documentation submitted by Applicants.

How does one submit a Marketing Authorisation assessment and what constitutes the documentation for a Marketing Authorisation assessment?

Common technical document



What documents constitute Modules 2/3/ 4/ 5?

AWTORITÀ DWAR IL-MEDIĊINI

Module 2	
2.1	OVERALL CTD TABLE OF CONTENTS OF MODULES 2, 3, 4, AND 5
2.2	INTRODUCTION
2.3	QUALITY OVERALL SUMMARY
2.3.S	DRUG SUBSTANCE
2.3.S.1	General Information
2.3.S.2	Manufacture
2.3.S.3	Characterization
2.3.S.4	Control of Drug Substance
2.3.S.5	Reference Standards or Materials
2.3.S.6	Container Closure System
2.3.S.7	Stability
2.3.P	DRUG PRODUCT
2.3.P.1	Description and Composition of the Drug Product
2.3.P.2	Pharmaceutical Development
2.3.P.3	Manufacture
2.3.P.4	Control of Excipients
2.3.P.5	Control of Drug Product
2.3.P.6	Reference Standards or Materials
2.3.P.7	Container Closure System
2.3.P.8	Stability

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Module 2 (Cont.)	
2.3.A	APPENDICES
2.3.A.1	Facilities and Equipment
2.3.A.2	Adventitious Agents Safety Evaluation
2.3.A.3	Novel Excipients
2.3.R	REGIONAL INFORMATION
2.4	NONCLINICAL OVERVIEW
2.4.1	Overview of the Nonclinical Testing Strategy
2.4.2	Pharmacology
2.4.3	Pharmacokinetics
2.4.4	Toxicology
2.4.5	Integrated Overview and Conclusions
2.4.6	List of Literature Citations
2.5	CLINICAL OVERVIEW
2.5.1	Product Development Rationale
2.5.2	Overview of Biopharmaceutics
2.5.3	Overview of Clinical Pharmacology
2.5.4	Overview of Efficacy
2.5.5	Overview of Safety
2.5.6	Benefits and Risks Conclusions
2.5.7	References

Module 2 (Cont.)	
2.6	CONTENT OF NONCLINICAL WRITTEN AND TABULATED SUMMARIES
2.6.1	Introduction
2.6.2	Pharmacology Written Summary
2.6.3	Pharmacology Tabulated Summary (Appendix B)
2.6.4	Pharmacokinetics Written Summary
2.6.5	Pharmacokinetics Tabulated Summary (Appendix B)
2.6.6	Toxicology Written Summary
2.6.7	Toxicology Tabulated Summary (Appendix B)
2.7	CLINICAL SUMMARY
2.7.1	Summary of Biopharmaceutics and Associated Analytical Methods
2.7.2	Summary of Clinical Pharmacology Studies
2.7.3	Summary of Clinical Efficacy
2.7.4	Summary of Clinical Safety
2.7.5	References
2.7.6	Synopses of Individual Studies

Module 3	
3.1	MODULE 3 TABLE OF CONTENTS
3.2	BODY OF DATA
3.2.S	DRUG SUBSTANCE
3.2.S.1	General Information
3.2.S.2	Manufacture
3.2.S.3	Characterisation
3.2.S.4	Control of Drug Substance
3.2.S.5	Reference Standards or Materials
3.2.S.6	Container Closure System
3.2.S.7	Stability
3.2.P	DRUG PRODUCT
3.2.P.1	Description and Composition of the Drug Product
3.2.P.2	Pharmaceutical Development
3.2.P.3	Manufacture
3.2.P.4	Control of Excipients
3.2.P.5	Control of Drug Product
3.2.P.6	Reference Standards or Materials
3.2.P.7	Container Closure System
3.2.P.8	Stability

Module 3 (Cont.)	
3.2.A	APPENDICES
3.2.A.1	Facilities and Equipment
3.2.A.2	Adventitious Agents Safety Evaluation
3.2.A.3	Novel Excipients
3.2.R	REGIONAL INFORMATION
3.3	LITERATURE REFERENCES

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Module 4	
4.1	MODULE 4 TABLE OF CONTENTS
4.2	STUDY REPORTS
4.2.1	Pharmacology
4.2.2	Pharmacokinetics
4.2.3	Toxicology
4.3	LITERATURE REFERENCES

AWTORITÀ DWAR IL-MEDIĊINI

Module 5	
5.1	MODULE 5 TABLE OF CONTENTS
5.2	TABULAR LISTINGS OF ALL CLINICAL STUDIES
5.3	CLINICAL STUDY REPORTS
5.3.1	Reports of Biopharmaceutic Studies
5.3.2	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials
5.3.3	Reports of Human Pharmacokinetic (PK) Studies
5.3.4	Reports of Human Pharmacodynamic (PD) Studies
5.3.5	Reports of Efficacy and Safety Studies
5.3.6	Reports of Post-Marketing Experience
5.3.7	Case Report Forms and Individual Patient Listings
5.4	LITERATURE REFERENCES

Clinical

a) Literature References

b) Bio Study Report

- Bio study report
- Bio study analytical report
- Bio study analytical validation report

Importantly, information from Modules 3/ 4/ 5 feed into the Summary of Product Characteristics

Module 3- Section 2,3

Module 4- Section 5.1/ 4.6

Module 5- All of Section 4/5.2

So how do we access Marketing Authorisation Assessments?

The process of granting a marketing authorisation application is a legal scientific activity, where an assessment report needs to be written in the appropriate detail to withstand legal scrutiny (especially in court).

My opinion: assessment is a similar activity to peer-reviewing publications for International Scientific journals ensuring that legal/guideline/pharmacopeial standards are implemented by applicants, Improtantly scientific interpretation of the conclusions presented by companies essentially involves a lot of 'thought' by the assessor.

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1. Get to know you product!!

An example: For the registration of Risperidone ask your self what do you need to support a Marketing Authorisation application?

Both parent and metabolite are active, therefore I would expect a BE study to test for both parent and metabolite.

- Which strength needs o be tested? Highest or lowest?
- Which is most sensitive strength to be tested in a BE study that is adequately powered to identify formulation differences? The choice depends if the PK profile for absorption that is linear or non- linear for the parent or active.

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2. Get information on the Reference Product (National vs. EU Ref product)

- Usually the Summary of product characteristics of reference product.
- Standard Reference Medical text books like the DSM-IV, Diagnostic Safety Manual- IV.
- Other Assessment Reports on ongoing DCP/ MRPs or ones that have been recently finalised.

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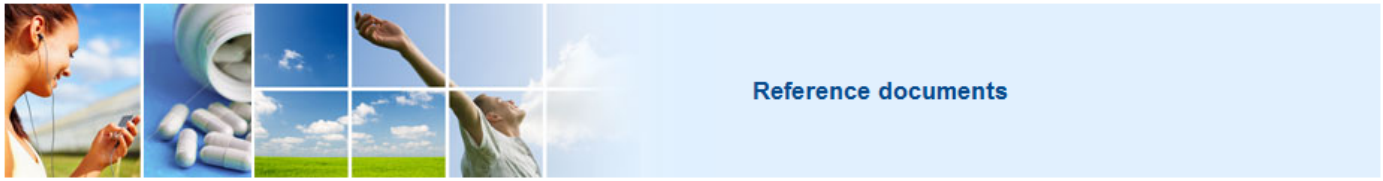
3. Get documentation (continued)

- Check the European Commission website- community register for the outcome of any EU wide Referral on Risperilone.

- Check the Heads of Medicines Agencies website for:
  - Any recommendations from the Pharmacovigilance working party on safety updates to the SmPC
  - The EU- harmonised birth late for Periodic Safety update report submissions

- Check the EMA's Pharmacovigilance Tracking Tool for issues/ risks being tracked at an EU level on Risperidone.

- Get other SmPCs from www.maltamedicineslist.com.



Reference documents

Reference documents

- EU Legislation - Eudralex
- Community Register
- Pharmaceutical Committee
- Case Law
- Pharmaceuticals Archives

Useful links

EU centralised procedures

Community Register of medicinal products for human use *

Active	By EU number	Alphabetical
Withdrawn or suspended	By EU number	Alphabetical
Refused		Alphabetical

Community Register of orphan medicinal products for human use **

Active	By EU number	Alphabetical
Withdrawn or suspended	By EU number	Alphabetical
Refused		Alphabetical

Community Register of veterinary medicinal products ***

Active	By EU number	Alphabetical
Withdrawn or suspended	By EU number	Alphabetical
Refused		Alphabetical

EU Referrals

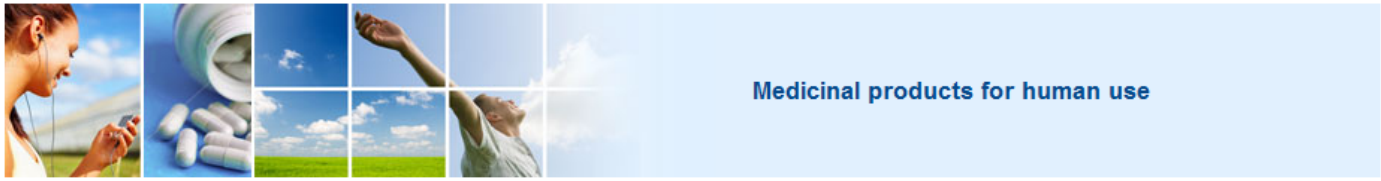
Human medicinal products	Alphabetical
Veterinary medicinal products	Alphabetical

List medicinal products authorised under Article 126a

Adopted Commission Decisions of the last six months

Human medicinal products by ATC

General index on active ingredient



Human referrals

Actilyse - Alteplase [Referral] - 30 Sep 2002
Actira 400 mg film coated tablets and associated names - Moxifloxacin [Referral] - 14 July 2008
Activelle [Referral] - 11 Sep 2008
Adartrel - Ropinirole [Referral] - 3 Apr 2006
Aggrastat - Irbesartan [Referral] - 18 Jun 1999
Agopton - lansoprazole [Referral] - 13 Dec 2006
Agreal - Veralipride [Referral] - 1 Oct 2007
Alendronate Hexal - alendronic acid [Referral] - 13 Apr 2007
Alendros 70 - alendronate sodium trihydricum [Referral] - 2 May 2007
Alvesco - ciclesonide [Referral] - 11 July 2008
Amaryl - Glimepiride [Referral] - 29 Aug 1996
Amfepramone - Amfepramone [Referral] - 9 Dec 1996
Amlodipine Wörwag - Amlodipine maleate [Referral] - 27 Apr 2004
Amlovita - Amlodipine maleate [Referral] - 26 Apr 2004
Antiadiposo - iodocasein/ thiamine nitrate - iodocasein / thiamine nitrate [Referral] - 26 Jan 2010
Aprotinin - Aprotinin [Referral] - 15 Feb 2008
Arcoxia and associated names - Etoricoxib [Referral] - 9 Sep 2008
Arimidex - Anastrozole [Referral] - 6 Nov 2009
Artirem - gadoteric acid [Referral] - 29 Mar 2005
Atacand and associated names - candesartan cilexetil [Referral] - 13 July 2010
Atacand Plus and associated names - candesartan cilexetil/ hydrochlorothiazide [Referral] - 16 Sep 2010
Atifor Chiesi 12 mcg - formoterol [Referral] - 11 May 2009
Atorvastatin - Atorvastatin [Referral] - 22 May 2006
Augmentin - amoxicillin/clavulanic acid [Referral] - 19 Oct 2009
Avalox - moxifloxacin hydrochloride [Referral] - 2 Oct 2009
Avalox 400mg film coated tablets and associated names - Moxifloxacin [Referral] - 14 July 2008
Belanette - Drospirenone + Ethinylestradiol [Referral] - 17 Jun 2008
benfluorex - benfluorex [Referral] - 14 Jun 2010
Beriate P - Human coagulation factor VIII [Referral] - 1 Dec 2003
Betavert N and associated names - betahistine dihydrochloride [Referral] - 2 Jun 2009

Printable version

Malta Medicines List

Help

What is the Malta Medicines List?

Use the drop down boxes and the text boxes to search and the filters to narrow down the number of records. Click the button for text search.
You can show / hide sections by clicking on the buttons.
The information contained in this list and in the SmPCs and package leaflets is for general information purposes only and thus the information in the list and the published product information should not be used officially as a substitute for the Marketing Authorisation legal documents held by the Marketing Authorisation Holders

Search

Therapeutic Class:	<Select One>	
ATC Code:	<Select One>	
Active Ingredients:	<Select One>	
Product Name:	<Select One>	
Pharmaceutical Form:	<Select One>	
Classification:	<Select One>	
Authorisation Number:		
Licence Number:	<Select One>	
Licence Holder Name:	<Select One>	
Licence Holder Address:	<Select One>	

1 of 12824 | Display Record: 1 Export

Record Id: 1

Therapeutic Class:	VITAMINS
ATC Code:	A11CC03
Active Ingredients:	Alfacalcidol 1mcg
Product Name:	One-Alpha
Pharmaceutical Form:	CAPSULE
Classification:	PoM
Authorisation Number:	AA244/17701
Licence Number:	PL0043/0050
Licence Holder Name:	P & D Pharmaceuticals Limited
Licence Holder Address:	38, Woolmer Way, Bordon Hampshire GU35 9QF, United Kingdom
Patient Information Leaflets:	View Documents

Please note that not all searches retrieve the product information

Links

- Malta Medicines Authority
- Glossary of Terms
- Know Your Medicines
- Summary of Product Characteristics

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Version: 1.0.3

Before you start…..

- Go to EMA website and download latest guidelines and Assessment reports template.
- Go to EMA website and download guidelines on Bioequivalence (BE) and Questions and Answers document on BE.

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

About CMDh
Statistics
Press Releases
Procedural Guidance
CMDh-Referrals
Product Information
PhVWP Recommendations
CMDh Recommendations
Harmonisation of SPCs - Article 30 Referrals
Core SPC/PL
Advice from CMDh
Templates
CMD subgroups / working groups
Paediatric Regulation
Questions & Answers
Contact Form
Contact Points
What's new history

- **For further details, please see the relevant PhVWP Monthly Report and the related Publication Policy published on the EMEA website under CHMP Pharmacovigilance Working Party**

Risk of psychiatric adverse drug reactions to inhaled and intranasal corticosteroids and risk of non-psychiatric systemic adverse drugs reactions to intranasal corticosteroids

- **Agreed wording in SPC and PL**
  Click here

Long-Acting Beta Agonists (LABAs) - Increased risk of exacerbation of asthma symptoms

- **Agreed wording in SPC and PL**
  Click here

Tamoxifen and the risk of variability in clinical response due to CYP2D6 genetic variants or when given with CYP2D6 inhibitors

- **Agreed wording in SPC and PL**
  Click here

Alendronate and the risk of oesophageal cancer

- **Agreed wording in SPC and PL**
  Click here

Camphor containing ointments and risk of unintented oral ingestion

- **Agreed wording in SPC and PL**
  Click here

Rosuvastatin and higher incidence of diabetes mellitus and gluscose metabolism disorders in healthy individuals

Human medicines
- Pre-authorisation
- Post-opinion
- Post-authorisation
- Product information
- Scientific advice and protocol assistance
- Scientific guidelines
  - Quality
  - Q&A on quality
  - Biologicals
  - Non-clinical
  - Clinical efficacy and safety
    - Clinical pharmacology and pharmaco-kinetics
    - Alimentary track and metabolism
    - Blood and blood forming organs
    - Blood products
    - Cardiovascular system
    - Dermato-logicals

Home ▸ Regulatory ▸ Human medicines ▸ Scientific guidelines ▸ Clinical efficacy and safety ▸ Clinical pharmacology and pharmaco-kinetics

Clinical efficacy and safety: Clinical pharmacology and pharmacokinetics

Email a friend | Print page | Help

If you have comments on a document which is open for consultation, please use the scientific guidelines. Form for submission of comments on

Topic	Documents	Reference number	Publication date	Effective date	Remarks
Use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products	Draft guideline Concept paper	EMA/CHMP/37646/2009	Release for consultation Apr 2010		Deadline for comments 31 Oct 2010
Investigation of drug interactions	Adopted guideline Draft guideline Concept paper	CPMP/EWP/560/95/Rev. 1 – Corr.	Release for consultation Apr 2010		Deadline for comments 31 Oct 2010
Investigation of bioequivalence	Overview of comments Adopted guideline Draft guideline Concept paper Concept paper	CPMP/EWP/QWP/1401/98 Rev. 1	Jan 2010	1 Aug 2010	
Questions & Answers: Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmacokinetics	Adopted guideline	EMEA/618604/ Rev. 2	Aug 2010		
Validation of bionanalytical methods	Draft guideline Concept paper	EMEA/CHMP/EWP/192217/09	Release for consultation Dec 2009		Deadline for comments 31 May 2010
Clinical Investigation of the	Overview of comments	CPMP/EWP/8	Feb 2007	31 Jul 2007	

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

enter search phrase search

generate PDF-Version of this page

Home | HMA Joint | **Human Medicines** | Veterinary Medicines

Heads of Agencies | **CMD(h)** | MRI Product Index | Directory

You are here: Human Medicines > CMD(h) > Templates > AR > DCP (AR/Comments)

- About CMDh
- Statistics
- Press Releases
- Procedural Guidance
- CMDh-Referrals
- Product Information
- Advice from CMDh
- **Templates**
  - QRD
  - AR
    - **DCP (AR/Comments)**
    - MRP
    - Renewals
    - Variations
    - Art 61.3 Procedure
    - Public AR
    - Paediatric Data
  - Applications for MA
  - Art.29 Referrals
  - Variations
- CMD subgroups / working groups
- Paediatric Regulation

Templates - DCP (AR/Comments)

In order to view some of the documents on this website you need **Acrobat Reader** (click here to download)

Non Clinical / Clinical AR for Generics - MRP & DCP
.doc / .dot
Last update February 2008

D70 Preliminary AR

Overview

.doc / .dot
Last update July 2009

Quality

.doc / .dot
Last update September 2010

Active Substance Master File (ASMF) AR
.doc / .dot

Non-clinical

.doc / .dot

Clinical

Risperidone

- Risperidone is a benzisoxasole derivative with an active metabolite, 9-hydroxy-risperidone. It is a second generation antipsychotic agent which combines potent serotonin 5-HT2 and dopamine D2 receptor antagonism. It has been shown to be effective against both positive and negative symptoms of schizophrenia and to have fewer extra-pyramidal side-effects than conventional antipsychotics.

- It is indicated in the treatment of:
  - Chronic schizophrenia including acute exacerabations
  - Chronic aggressive or psychotic symptoms of dementia
  - Manic episodes in bipolar disorders

- Impulse control disorders with aggression or harm to self or others in patients with reduced intelligence.

Generics

“BIOAVAILABILTY AND BIOEQUIVALENCE ASSESSMENT”

- Pharmaceutical equivalence : Medicinal products are pharmaceutically equivalent if they contain the same amount of same active substance(s) in the same dosage forms that meet the same or comparable standards.

- Pharmaceutical equivalence might not imply bioequivalence as differences in excipients and or manufacturing process can lead to faster/slower dissolution and/or absorption.

- Pharmaceutical alternatives – same active substance with different salts/ester, etc.

- Bioavailability – rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action (i.e. general circulation)

- Absolute bioavailability = comparison of dosage form vs IV

- Relative bioavailability = 1 dosage form vs another (tablets vs oral solution)

Bioequivalent if two medicinal products are:-

1. pharmaceutical alternatives or pharmaceutical alternatives

2. bioavailability is the same (i.e. rate and extent + safety + efficacy)

Types of Bioavailability studies

1. Pharmacokinetic

2. Pharmacodynamic with clinical end points (say for example local topical applications)

3. In vitrio studies with appropriate justification

Essentially Similar Products

A medicinal product is essentially similar to an original product where it satisfies the criteria of having the same:

- Qualitative and quantitative composition in terms of active substance.
- Pharmaceutical form
- Bioequivalent
- Safety and efficacy

Therapeutically Equivalent

1. Contains the same active substance and therapeutic moiety

2. Shows same efficacy and safety

Bioequivalence most appropriate method of substantiating therapeutic equivalence between medicinal products.

Cases where similar extent of absorptions but different rates of absorption are observed the products can still be judged therapeutically equivalent if those differences are not of therapeutic relevance

A CT will be needed!

Guidelines

EMEA (EU)

- Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98

- Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation) CPMP/EWP/280/96

Continues…

Guidelines (continues)

WHO:

- Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products / Regulatory Support Series, No 5 (WHO/DMP/RGS/98.5).

Guidelines (continues)

- Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (FDA, March 2003)
- Guidance for Industry: Bioequivalence Guidance (FDA, October 9, 2002)
- Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies – Part A: Oral Dosage Formulations Used for Systemic Effects (Canada, 1992)

Immediate release product

- Preparations showing a release of the active substance(s) which is not deliberately modified by a special formulation design and/or manufacturing method:

  - tablets
  - capsules

Immediate release product

- Usually a single dose study in fasting state is adequate.

- If the application contains several strengths of the active substance, bioequivalence study only with one strength may be acceptable→ dissolution profiles with each strength.

- If food enhances or interferes with drug absorption, a bioequivalence study in fed state should be performed.

Immediate release product

- If label indicates 'should be administered in fed or fasting state' then bioequivalence study should be performed accordingly.

- A single dose study at a higher than approved dose may be appropiate for certain drugs (→ difficulties in bioanalytics).

The amount of bioequivalence studies with preparations containing several strengths

❖ If the application contains several strengths of a immediate release oral dosage form bioequivalence study only with one strength may be acceptable. The following conditions should be fulfilled:

- The products are manufactured by the same manufacturer and process
- Qualitative composition of the different strength is the same

Continues…

The amount of bioequivalence studies with preparations containing several strengths

- Ratio between amounts of active substance and excipients is the same (or in case of preparations containing low concentration of the active substance; <5 %; the ratio between amount of excipients is similar)
- The dissolution profiles of the test products are similar
- The drug input should be linear over the therapeutic dose range

Design and Conduct of BE Study

1. GCP
2. Ethical approval

- The study is a comparative bioavailability study designed to establish equivalence between test and reference products.

Design of BE Study

1. Important that the effect of the formulation can be distinguished.

2. For a comparison of two medicinal products, a 2-period, 2-sequence crossover design is best.

If all subjects receive two treatments in the same order, observed differences between treatments would be confounded with any other changes that occur over time. For example in a study on cholesterol, subjects might change diet and exercise. This might affect cholesterol levels that might be attributed to the second treatment.

2-period, 2-sequence crossover design

- ½ of subjects receive treatment A followed by treatment B
- ½ of subjects receive treatment B followed by treatment A
- Parallel designs can be considered for active ingredients with a long t½
- Single dose studies usually suffice
- Steady-state studies may be required in case of:-
  1. Dose or time dependant pharmacokinetics
  2. Modified release products
  3. Problems of sensitivity to quantify plasma concentrations after a single dose
  4. Intra-individual variability in plasma concentration, as disposition does not help in demonstrating bioequivalence in a single dose study and this variability is reduced at steady state.

Number of subjects determined by:

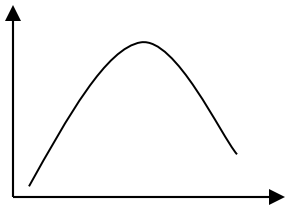
- Error of variance associated with the primary characteristic to be studied as estimated from a pilot experiment.
- Significance level desired.
- Expected deviation from the reference product.
- Required power.

Number of points should be > 12

- Treatments should be separated by adequate wash out in SS. The washout in previous treatment can overlap with the build-up of the second treatment, provided the build up period is sufficiently long (at least 3 x the t½).

- Sampling schedule planned to provide correct estimation of Cmax

- Reliable estimate of terminal half-life it is to be collected 3-4 samples during the terminal log linear phase.



Subjects

Selection Criteria:-

- Minimise variability
- Healthy volunteers
- Include/exclude criteria in the protocol
- Risk to child bearing potential considered
- Age 18 – 55
- Normal BMI
- Screened to clinical lab tests

- In most cases, measurement of active ingredient is carried out but sometimes of the metabolite (if there are difficulties in measuring the active ingredient), justification required.

- Parameters measured

AUCt, AUC∞, Cmax, Tmax, t½

for studies in steady state

AUCt, Tmax, Cmin and fluctuation $\left(\frac{Cmax - Cmin}{Cav} \right)$

AUCt is the most reliable reflection of the extent of absorption.

Chemical Analysis

Bioanalytical methods should be characterised by GLP.

1. Stability for stock solutions and analytes during entire period of storage.
2. Specificity
3. Accuracy
4. Precision
5. Limit of quantification
6. Response function

Calibration for each analyte.
SOPs

Data Analysis

To quantify the difference in bioavailability between A and B and demonstrate that clinically important difference is unlikely.

Stats

Stats method for testing relative bioavailability is based upon the 90% confidence interval for the ratio of the population means (test/reference) for parameters under consideration.

i.e. 2-one-sided test procedure with null hypothesis of bioinequivalence of 5%

Analysis is using ANOVA.

Acceptance ranges

AUC ratios and Cmax ratio 90% CIs with acceptance interval of 0.8 – 1.25.

If product has a narrow therapeutic range tighter.

Others Stat evaluation of tmax only makes sense if there is a clinically relevant claim for rapid release or AEs.

Case Study 10

EMEA/H/A-xx/xx
Referral

CHMP outcome

XXX YY – CMDh referral

Scope

- Referral under article 29(4) of directive 2001/83/EC as amended.
- Concerns XXX 70 mg containing 70 mg Alendronate.
- Referred to the CHMP by the RMS following potential serious risk to public health raised by 1 MS.

Scientific Discussion

- 3 Questions were put forward to the company.
- Qs focus on Efficacy, Safety and Quality.

Scientific Discussion

Q1

- The Applicant/MAH has conducted a BE study to support the MA of the generic alendronate product (XXXX YY). The CI of the AUC difference of cumulative urinary excretion (Ae0-36) between XXXX YY and the reference product is 105.57 – 129.34%. The Applicant should justify that, based on the results presented, XXXX YY can be considered bioequivalent to the reference product (Fosamax MSD).

Scientific Discussion

Applicant response:

- Alendronate (a member of the bisphosphonates class) has a very low bioavailability (approx 0.6%), long and not fully determined $t_{1/2}$ estimated at 10 years.

- Slow bone remodeling suggestive that difference in systemic exposure is of no clinical significance.

- Absorbed Alendronate is partially retained in the skeleton (for a long time) and the rest is eliminated by renal excretion.

Scientific Discussion

Applicant response:

- The effects of pH-increasing agents or whether given 30 min – 2 hours prior to a meal are indistinguishable, and the observed BA may be decreased by 40 % leading to a BE of 0.36. (studies and SmPC of Fosamax). This seems to have no clinical relevance.

- The results of the BES show that XXX YY AUC lies in the 105.57%-129.34% CI. Leading to changes in absorption of 0.48-0.75. The real difference in absorption (if any) in the observed study is 0.026% above the narrow upper limit. This is unimportant taking into account the food effect.

Scientific Discussion

Applicant's Response

- Taking into account that the treatment of osteoporosis is chronic.
- Alendronate acts as a specific inhibitor of osteoclast-mediated bone resorption, and has sustained reduction of biochemical markers of bone remodeling resulting in lower vertebral fractures. Dose-dependent inhibition of bone resorbption, including decreases in markers of bone collagen degradation.
- Biochemical changes tend to return towards the baseline values as early as 3 weeks after discontinuation of treatment.

Scientific Discussion

Assessment on the applicant's response :

- The clinical relevance in the deviation of the accepted BE CI criteria were not discussed.

- The Applicant does not discuss whether the 2 products are BE.

Scientific Discussion

- Data from the BES yield point estimates (90% CI) of AUCe of 116.9% (105.57%-129.34%) and for Rmax of 115.5% (105.19%-126.74%) – Outside the acceptance limits

- Widening of the CI was mentioned in the protocol for Rmax but not for AUCe. The absence of a prospective discussion for widening acceptance criterion leaves room for **data driven analysis**

- The applicant points out that the failed BE might be probably due to variability. The %CV of 38% and 35% for AUCe and Rmax respectively were expected. Based on these expectations the applicant included n=80 for the BES in order to cope with the high CV. Therefore the high %CV does not provide an explanation for missing the acceptance criterion with this properly sized BES.

Scientific Discussion

- Other generics met these CIs!
- Bioequivalence as per EU guideline has not been demonstrated

Scientific Discussion

Q2

- Whether the observed differences in outcomes of the BES between tested and reference product is of concern to increased incidence of AEs being thus PSR to PH?

Scientific Discussion

Applicants response

- Alendronate produces GI AEs. The GI AEs of bisphosphonates have been well documented. They occur in up to 30% of patients and are due to the local irritation of the GI by alendronate. The GI AEs can occur within 30 min of the dosage being ingested.

- XXX YY is ingested once a week and has a better GI Safety profile than alendronate 10 mg preparations.

- The small difference in BES of XXXX YY could therefore, not be associated with higher incidence of AEs.

Scientific Discussion

- The applicant provides in my opinion sound clinical argumentation, however he does not satisfy the legal regulatory perspective.

Scientific Discussion

- AEs are likely to occur for both the reference and tested products.
- The registration of a generic is based on the data from the originator. The aim of the BES is to allow data from the innovator dossier to be also applicable to the generic, in such a way to ensure that efficacy and safety of generic is comparable with that of the innovator.
- Generics should be interchangeable with the innovator product in order to be switched according to the policy for subscription of generics in many EU MSs. BE is fundamental in order to establish inter-changeability. This was recognised by the Applicant by having an acceptance range of 0.8 to 1.25 for Ae as predefined in the protocol. Therefore, post-hoc deviation from the relevant guideline is not acceptable.

Scientific Discussion

Q3

- Do the differences in excipients in the product formulations of XXX YY and the reference product have an influence on the safety profile of XXXX YY?

Scientific Discussion

Applicant's Response:

- Differences in excipients do not explain the results: the disintegrants Croscarmellose Sodium (Fosamax) and Maise Starch (XXX YY) – are widely used excipients in line with the Ph Eur. The concentrations of these disintegrants in tablets are pre determined in the Ph Eur monograph and these were followed by the company. The company also explains that pH will also have no effect on the disintegration time.

- Disintegration/Dissolution studies were conducted by the company with different batches of both test and reference product. The results indicate that for both formulations the submitted data on dissolution shows that the product for registration has comparable properties compared to the reference product. The dissolution profile show that the tablets dissolve fast (>85% after 15 min) in the in-vitro situation.

Scientific Discussion

Assessment

- The excipients are widely used and common. Use of starch is acceptable.
- Mannitol is also used as a diluent, use of this excipient can result in decreased gastric emptying which can affect BE. However, in the concentration that mannitol has been used (10-90% w/w of a 100mg tablet!!!) such an effect is not expected.
- The dissolution studies show that test and reference products are comparable.
- From a quality perspective no problems with safety and BA.

Outcome of referral

- Adequate proof of BE between XXX YY and the innovator Fosamax 70 is lacking. The calculated 90% CI for the urinary parameter A_{36h} was 105.57-129.34 i.e. outside the predefined and appropriate 0.80 – 1.25 criterion. According to the CHMP NfN CPMP/EWP/QWP/1401/98, widening of the acceptance range should be prospectively defined based on relevant data. Post-hoc widening of the acceptance range for the 90% CI for Ae, as proposed by the applicant is considered data driven analysis and therefore not acceptable.

Thank You

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