







MRP & DCP

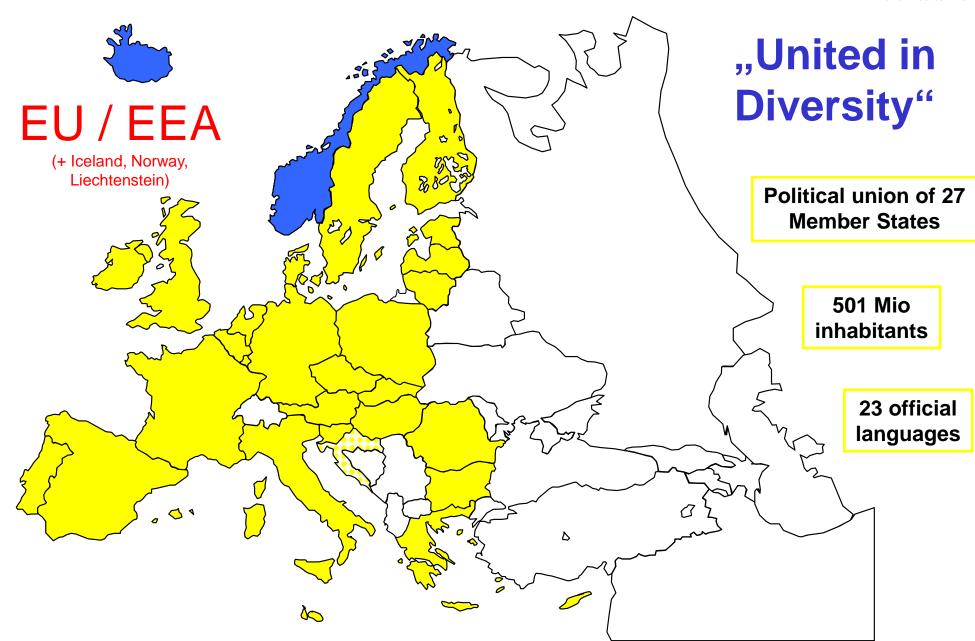
step by steb instructions how to apply and how the procedures are conducted

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Types of MA in the EU/EEA

central



MA valid for the EU

national



MA valid for a single EEA-MS



National Marketing Authorisation MRP and DCP

Scope



Scope of MRP/DCP: National Marketing Authorisation - (1)

- new active substances (if not mandatory for the centralised procedure)
- known active substances under Article 8(3)
- biological medicinal products (incl. biosimilar) (if not mandatory for the centralised procedure)
- generic medicinal products to national (and centralised) authorised reference medicinal products
- well established use (WEU) ("bibliographic applications")



Scope of MRP/DCP: National Marketing Authorisation - (2)

cont.

- known active substances in new combination
- informed consent to national MA
- (line) extension applications to national authorisations
- homeopathics
- traditional herbal medicinal products



Where to apply for a national MA?



Competent Authority (CA) of a Member State (MS) of the EU/EEA

Who will grant a national MA?



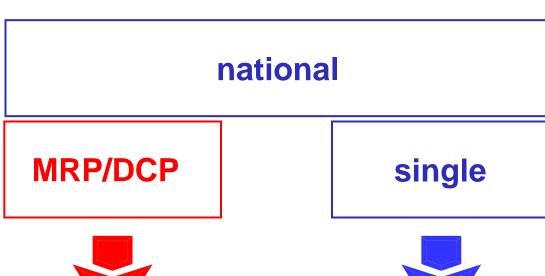


Procedures for a MA-Application

central



one MA valid for the EC









MRP and **DCP**



What is the Mutual Recognition Procedure (MRP) and the Decentralised Procedure (DCP)?

 describes the procedure to get national MAs in MSs of the EEA for the same medicinal product

mandatory procedures

work sharing between MS



Article 17 of Directive 2001/83/EC

"1....

- Applications for marketing authorisations in two or more Member States in respect of the **same medicinal product** shall be submitted in accordance with Articles 27 to 39.
- 2. Where a Member State notes that another marketing authorisation application for the same medicinal product is being examined in another Member State, the Member State concerned shall decline to assess the application and shall advise the applicant that Articles 27 to 39 apply."



Article 18 of Directive 2001/83/EC

"Where a Member State is informed in accordance with Article 8(3)(1) that another Member State has authorised a medicinal product which is the subject of a marketing authorisation application in the Member State concerned, it shall reject the application unless it was submitted in compliance with Articles 27 to 39."



Same medicinal product?

- Same qualitative and quantitative active ingredient
 - There may be the differences in excipients provided that there is no impact on safety and efficacy
- and > Same pharmaceutical form, but ...
- **and** > Link between companies
 - all legal entities
 - all license holders
 - companies who have agreed to act in a concerted actionMRP/DCP

(Commission Communication July 1998)



MRP and DCP - (1)

Two routes to receive a MA for the same medicinal product

1. Mutual recognition procedure (MRP)

where the medicinal product has already received in a MS a MA at the time of application

or

2. Decentralised procedure (DCP)

where the medicinal product has <u>not</u> received in a MS a MA at the time of application



MRP and DCP - (2)

MRP – Interpretation (RMS): (with regard to 'the medicinal product' and 'duplicate application')

1. You have to use the first national MA for the MRP

or

2. You need a national MA to start the MRP, but you don't have to use an existing MA (submission of an "updated copy"-application for DCP)



MRP and DCP - (3)

'CMDh Recommendations on Multiple/Duplicate
 Applications in Mutual Recognition and Decentralised
 Procedures' (Rev 3, June 2007)

DEFINITION

As a duplicate is an independent authorised medicinal product, there is no definition of a "duplicate" in the pharmaceutical legislation. However, for practical purpose, a duplicate application is defined by reference to the first application or marketing authorisation as follows:

- same dossier (copy of modules 1, 2, 3, 4 and 5);
- same legal basis according to Directive 2001/83/EC, as amended;
- different tradename;
- same or different applicant/marketing authorisation holder.

CMDh Q&A No 1:

The CMDh has agreed that a duplicate application of a medicinal product authorised via the Mutual Recognition Procedure can be accepted via the Decentralised Procedure, provided that the same Reference Member State is used.



MRP and DCP

DCP (= Decentralised Procedure)



DCP - Overview

- 1. Pre-procedural Step
 - scientific/regulatory advice
 - validation
- 2. Assessment step I 120 days incl. clock-stop
- 3. Assessment step II 90 days
- 4. National step to grant MA 30 day incl. Public AR



DCP - flow chart - (1)

Revision 4, March 2013

1. Pre-procedural Step

Before Day - 14 Pre-submission discussions between Applicant and RMS

Day - 14 Submission of the dossier to RMS and CMSs Validation of the application



Pre-submission discussions

SLOTS !!!!!!

- tool for workplanning
- two models currently in use/discussion
 - -'continium'
 - -'quantum'

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DCP

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

- Decentralised Procedure Members States' Standard Operating Procedure (March 2013) [Track version]
- Recommendations on submission dates for Applicants of the DCP (November 2011)
- Recommendations on submission dates for Applicants of the DCP(October 2012)
- Flow chart of the Decentralised Procedure (March 2013) [Track version]

Requests to act as RMS in DCP

• Common request form for RMS (February 2009)

Templates

- Templates for Assessment Reports and Comments
- · Templates for referrals to CMDh

Links to NCAs webpages

Information on national timeslot booking systems and recommendations for requests to act as RMS (March 2012)



DECENTRALISED PROCEDURE - REQUESTS TO ACT AS RMS

Doc. Ref.: CMDh/020/2009/Rev11 March 2012

The Heads of Medicines Agencies' Task Force on Resources in DCP in cooperation with CMDh has developed a common request form to be used when asking a National Competent Authority (NCA) to act as Reference Member State in a decentralised procedure. The Heads of Medicines Agencies has agreed to publish the request form on the CMDh website as well as on all national competent authorities websites.

The request form (http://www.hma.eu/219.html) should be submitted to the NCA in accordance with information provided by that NCA. Below is a list of links to the NCAs' webpages where their recommendations for requests to act as RMS are published.

MEMBER STATES	SUMMARY OF NATIONAL BOOKING SYSTEMS & LINKS TO NATIONAL WEBPAGES
AUSTRIA	Applicants wishing to apply for a marketing authorisation through the Decentralised Procedure with AT as RMS are advised to inform AGES PharmMed in advance about their intentions and agree on a date for submission with AGES PharmMed. Requests for a time slot are made by using the CMDh request form. Completed forms should be sent to ms@aqes.at .
	For long-term planning twice a year AGES PharmMed provides "request windows" of one month each during which applicants are given the opportunity to apply for available time slots as indicated in the availability-matrix on the website: http://www.basq.at/en/medicines/authorisation/mrpdcp/aqes-pharmmed-slots/ .
	Requests for available slots because of short-term cancellations for the current and the following two quarters as indicated in the availability-matrix on the website:
	http://www.basq.at/en/medicines/authorisation/mrpdcp/ages-pharmmed-slots/ can be placed any time to ms@ages.at.
	For MR, Repeat-Use and Line Extension Procedures requests can be placed anytime to ms@aqes.at.
	Applicants are advised to inform AGES PharmMed as early as possible if an agreed application will not be submitted in due course to the slot agreed.
	More detailed information can be found on the AGES PharmMed website:
	http://www.basq.at/en/medicines/authorisation/mrpdcp/ages-pharmmed-slots/.



... current problems

- high number of cancellations or delays
 - 54 % with 34 % total cancellation
 - ongoing discussion with trade associations

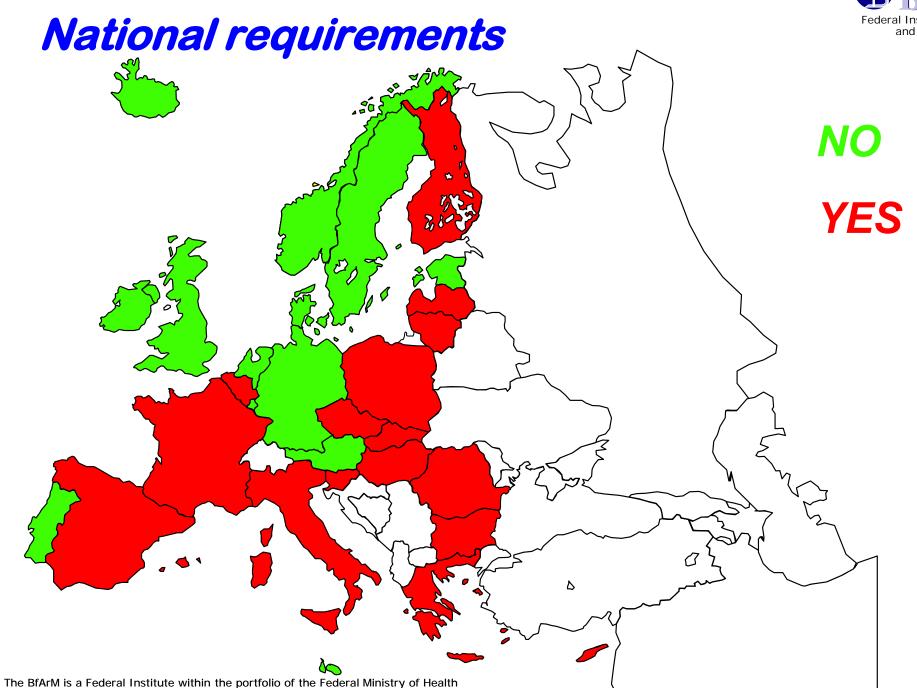


Validation – (1)

- Administrative validation (!) therefore no validation of the content of the application
- Reduction of national requirements

a lot of effort – but not totally sucessful Still additional national requirements for some of the MSs







Validation – (2)

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eSubmissions

Validation Procedure

- Member state agreement upon conditions under which the RMS can start MRP/DCP (October 2012) [Track version]
- Procedural advice: Automatic validation of MR/Repeat-use/DC Procedures (March 2012) [Track version]
- Additional Data requested for New Applications in the Mutual Recognition and Decentralised Procedures (September 2011) [Track version]
- Common Grounds for Invalidation/Delaying Validation (September 2010)
 [Itack version]
- Member States Recommendations on the Cover Letter for New Applications submitted through Mutual Recognition and Decentralised Procedures (March 2012)
 [Track version]
- CMDh Best Practice Guide on the compilation of the dossier for New Applications submitted through the Mutual Recognition and Decentralised Procedures (March 2008)

Introduction to Published Papers on Validation has been taken off the website as it was considered to be obsolete.



CMDh PROCEDURAL ADVICE ON VALIDATION ISSUES/NATIONAL REQUIREMENTS

COMMON GROUNDS FOR INVALIDATION/DELAYING VALIDATION*

- Application not received/modules are missing
- Missing/incorrect fee
- Application form/cover letter not signed/not signed with original signature
- The application form is incorrect (eg. information missing, incorrect type of procedure, legal basis incorrect, incorrect reference medicinal product, reference to an European reference medicinal product although there is a nationally authorised medicinal product)
- Documents in accordance with NtA, vol. 2B are missing or absence not justified (eq. Braille, Consultation with Target Patient Groups, Pharmacovigilance System, Environmental Risk Assessment, Specific Requirements for Different Application Types, Paediatric Regulation(where applicable))
- Annexes to the application form are missing or absence not justified (eg Declaration from the QP, TSE certificates for excipients of animal origin)
- Manufacturing licenses, GMP certificates and/or import licenses have not been updated or are missing. Proposed batch releaser is situated outside the EEA
- ASMF and/or letter of access to ASMF missing or incorrect version of the ASMF has been submitted
- Confirmation that identical dossiers are submitted in both RMS and the CMS is missing.

...



... progress



MEMBER STATE AGREEMENT UPON CONDITIONS UNDER WHICH THE RMS CAN START THE MRP/DCP

Doc. Ref.: CMDh/243/2011/Rev 5 October 2012

Two categories

- validation issues which prevent the start (closed list!) e.g. only national requirements which are published on the CMDh website
- procedure can be started, but non-validation issues has to be solved with day 60 response (MRP) or day 106 response (DCP) at latest



DCP - flow chart - (2)

2. Assessment step I – 120 days

Day 0	RMS starts the procedure and the assessment of the dossier
<i>Day 70</i>	RMS forwards PrAR, SmPC, PL and labelling to CMSs and Applicant
Day 100	CMSs send comments to RMS and Applicant RMS may consult CMS to close procedure
Day 105	RMS close the procedure or stops the clock



DCP - flow chart - (3a)

Clock-off period

 recommended period of 3 months, which could be extended for further 3 months and if justified



Reasons for long clock-stop ...

- on request from the applicant !!!
- new or additional BE-study/studies
- missing studies
- GMP / GCP inspection
- wait for the outcome of ongoing discussions
- •
- Don't Submit Premature Dossiers!
- Improve Quality of the Dossier!



DCP - flow chart - (3b)

Clock-off period

- recommended period of 3 months, which could be extended for further 3 months and if justified
- Applicant send draft response to RMS if not letter to RMS about the submission date of the final response
- Applicant agree with the RMS the date of submission of the final response
- Applicant submit final response document to MS



DCP - flow chart - (4)

Day 106 valid submission of the response of the applicant received

= Restart of the procedure

RMS updates PrAR to prepare draft AR (DAR), draft SmPC, draft PL and draft labelling

Day 120 if consensus – RMS close procedure if consensus not reached





DCP - flow chart - (5)

3. Assessment step II – 90 days

Day 120 RMS sends draft AR, draft SmPC, draft PL and draft labelling to CMSs and Applicant

Day 145 CMSs send (final) comments on draft AR, ...

Day 150 if consensus – RMS close procedure no consensus – RMS to dicuss items with applicant (and CMS) and prepare of a report on outstanding issues to the CMD (until Day 180)

Day 195 Break-out Session

CMSs send final comments



DCP - flow chart - (6)

Day 210 closure of the procedure

mutual approval

or

disagreement and referral to the Coordination Group (CMDh)

(based on 'potential serious risk to public health')



DCP - flow chart - (7)

4a. National step to grant MA – 30 days

Day 215 (95) Applicant sends national translations of SmPC, PL and labelling

Day 240 (120) granting of the national MA



This timeframe of 30 days is equally valid for the CMS in the MRP !!!



MRP and **DCP**

MRP RU-MRP (Repeat Use MRP)



MRP - flow chart - (1)

1. Validation

Before Day - 14 Submission of Dossier by Applicant to CMS

Submission of Assessment Report to CMS (and Applicant)

Day - 14 Start of the Automatic Validation

Def. "automatic": 'not against' is 'in agreement'



Why Validation Issues ?-(1)

CMDh –Procedural Advice on Repeat-Use (Rev. 7, July 2011)

Granted MA are with proofen safety and efficacy, but new application in the CMS !!!!

- > is the dossier still up-todate
 - changed Guidelines (e.g. bioequivalence)
 - new legislation (e.g. pharmacovigilance)
 - science still state of the art ?
- > status of the SmPC/PL?
 - are the indications state of the art?
 - patient consultation ?



Why Validation Issues ?-(2)

cont.

- > all (national) variation are finished?
- ongoing (national) renewal ?
- > still conditions to fulfil from the time of approval?
- (updated) assessment report available?
- change of assessor
- change of clinical philosopy
- prescription status ...



Why Validation Issues ?-(3)

- legal basis of the application (10a, 10b)
- outdated GMP- and CEP-certificates
- problems related with ASMF
- unknown GCP-problems

and therefore...

- an update is necessary before submission
- takes time and resources
- ... but no security against surprises during the MR-Procedure !!!



MRP - flow chart - (2)

2. The 90 Days-Procedure

Day 0	RMS starts the procedure
Day 50	CMS send comments to RMS and Applicant
<i>Day 58</i>	Draft "Applicant's Response Document = ARD"
•	to RMS
Day 60/68	Final ARD and "Assessor's Response
•	Document" (if applicable) to CMS
<i>Day 75</i>	CMS comments on ARD to RMS
•	Response of Applicant to CMS
	Possibility of a Break-out Session
	n-'comments and answers circles'



MRP - flow chart - (3)

Day 85 "finally proposed SmPC" to CMS

Final comments of CMS

Day 90 closure of the procedure

mutual approval

or

disagreement and referral to the Coordination Group (CMDh)

(based on 'potential serious risk to public health')



MRP - flow chart - (4)

if CMS

3. National step – 30 days

Day 95 Applicant sends national translations of

SmPC, PL and labelling

Day 120 granting of the national MA

if RMS:

3. update of the national MA + Public AR



Why update of the existing MA?

MRP

- changes to the dossier, SmPC, PL, labelling during the procedure
- need to update the existing national MA

Repeat-Use MRP

- Procedure only between RMS and new CMS
- no changes are possible during the procedure
 - yes or no-decision for the new MS
 - 'old' MS have to agree with changes
- MAH 'agree' to introduce the changes ask for via a variation



Public AR

Transparency of Marketing Authorisations

- MA and SmPC public available
- Public Assessment Report (PAR) is public accessible
 - without any information of a commercially confidential nature
 - a justification for each indication applied for shall be given
 - in MRP/DCP written and updated (Variations, Renewal) by the RMS for the CMS
 - Consultation between RMS and Applicant on the content of the PAR (CMDh-BPG)
- Summary in lay language



DCP - flow chart - (8)

4b. Public AR

(CMDh BPG FOR THE PUBLIC ASSESSMENT REPORT IN THE DECENTRALISED AND MUTUAL RECOGNITION PROCEDURE January 2006)

End of MRP (Day 90) or DCP (Day 210) = Day 0

<i>Day 10</i>	RMS send draft of PAR to Applicant
Day 20	comments on PAR to RMS
Day 25	- RMS to check answers of Applicant
_	- prepare final PAR
Day 60	- publication of the PAR on the website of the
•	Heads of Medicinal Agencies (HMA)

DMO and dueft of DAD to A and C



... http://www.hma.eu

HMA**

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Home

HMA Joint

Human Medicines

Veterinary Medicines

Welcome to The Heads of Medicines Agencies website

This is the common website for the human and veterinary medicines authorities in Europe.

HMA Joint

The Heads of Medicines Agencies is a network of the Heads of the National Competent Authorities whose organisations are responsible for the regulation of Medicinal Products for human and veterinary use in the European Economic Area. The Heads of Medicines Agencies is supported by working groups covering specific areas of responsibility and by the Heads of Medicines Agencies Management Group and Permanent Secretariat.

- HMA Management Group
- HMA-Topics
- Stakeholder Information

03/26/12

HMA Joint - Whats New

Annual Report 2011-2012 on the HMA Strategy

- Annual Report 2011-2012 on the HMA Strat... added
- 23-24 February 2012,
 Copenhagen (Denmark... added

Human Medicines

This channel provides information relating to the Heads of Agencies responsible for regulation of human medicinal products.

- Heads of Agencies
- CMD(b)
- MRI Product Index
- Directory
- Contact points for HMA and HMA-WGs
- · What's new history (6 months)



Veterinary Medicines

This channel provides information relating to the Heads of Medicines Agencies responsible for regulation of veterinary medicinal products.

- Heads of Agencies
- CMD(v)
- VMRI Product Index
- Directory
- . Contact points for HMA and HMA-WGs
- · What's new history (6 months)







... the new product index - (1)



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Start

This is the Start Page of the **Human** MRIndex

Search in database for the given term

Search Advanced Product Search

20 Latest Human Products

- Femoston 1/10
- Femphascyl 1/10
- Femoston 2/10
- Zolpidemtartraat 5 PCH
- Belfor 20 mg/5 mg
- Enriga
- Fluoxetine Capsules 20 mg
- Kaliumlosartan HCS 50 mg
- Belfor 40 mg/5 mg
- Kaliumlosartan HCS 100 mg
- Fluvastadiq
- Fluvastadiq
- Alterfast
- Alterfast
- Paclitaxin
- Spiriva 18 microgram
- Cefuroxime 250mg Film-coated Tablets
- Cefuroxime 500mg Film-coated Tablets
- Ylisapril comp.
- Kaliumlosartan HCS 25 MG

50



... the new product index - (2)

Details

Product Name in the RMS: Cefuroxime 500mg Film-coated Tablets

MR Number: UK/H/1699/003

Date of outcome: 26.11.2009

Type of application

Level 1:	Abridged
Level 2:	Additional Strength/Form
Level 3:	Generic
Level 4:	Chemical Substance
Level 5:	Prescription Only
Active Substances	cefuroxime
Form	Film coated tablet
Strength	500mg

MA Holder in the RMS TEVA UK LIMITED
RMS United Kingdom

Date of last change 14.05.2012

ATC-Code J01DC02 Cefuroxime

CMS Country	Domestic Product Name		
Czech Republic			
Ireland			
Italy			
Poland	Cefuroxime Teva		
Slovak Republic	Cefuroxim - Teva 500mg		
Spain			

De	ocum	ents
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PAR: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con071304.pdf (26.02.2010)

Export results to csv

Export results to excel



Safeguarding public health



Public Assessment Report Decentralised Procedure

Cefuroxime 125 mg Film-coated Tablets
Cefuroxime 250 mg Film-coated Tablets
Cefuroxime 500 mg Film-coated Tablets

PL 00289/1185 PL 00289/1186 PL 00289/1187

UK/H/1699/01-03/DC

TEVA UK Limited

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted TEVA UK Limited Marketing Authorisations (licences) for the medicinal products Cefuroxime 125 mg, 250 mg and 500 mg Film-coated Tablets (Product Licence numbers: PL 00289/1185-7). These medicines are available on prescription only.

Cefuroxime 125 mg, 250 mg and 500 mg Film-coated Tablets are antibiotics that belong to a class of medicines called cephalosporins. They are used to treat certain types of infections and work by killing certain types of bacteria.

Cefuroxime 125 mg, 250 mg and 500 mg Film-coated Tablets may be used to treat the following infections:

- Upper respiratory tract infections (including infections occurring in the ears, sinuses, tonsils and throat)
- · Chest infections such as bronchitis
- Bladder infections (water infections)
- Skin infections (recurring boils, ulcers and impetigo)
- Early Lyme disease (a rare infection caused by tick bites)

The data submitted in support of these applications for Cefuroxime 125 mg, 250 mg and 500 mg Film-coated Tablets raised no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.

Medicines and Healthcare products Regulatory Agency



... (new) development

- for historic reasons only positively concluded DCP are published 30 days after the end of the procedure (exemption: CMDh-Referral)
- new policy:
 - rejected DCP are published 30 days after closing of the procedure, starting 01. 09. 2012
 - list of involved MS will be published
 - negativ PAR will be published
- DCP-applications withdrawn after Day 120 will be published (in preparation)



