Extensions of indication in the European Union – a regulatory overview

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät
der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

Silvia Balogh
aus München

Bonn 2016

Betreuer und 1. Referent: Susanne Winterscheid

Zweiter Referent: Dr. Dr. Karl J. Krobot

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List of Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
AkdÄ	Arzneimittelkommission der deutschen Ärzteschaft (Drug Commission of the German Medical Association)
AMD	Age-related macular degeneration
AMNOG	Arzneimittelmarktneuordnungsgesetz
AM-NutzenV	Arzneimittel-Nutzenbewertungsverordnung
ÄndG	Änderungsgesetz

API	Active pharmaceutical ingredient
Article 8(3)	Article 8(3) of Directive 2001/83/EC
Article 10(3)	Article 10(3) of Directive 2001/83/EC
(B-)CLL	(B-cell) chronic lymphocytic leukemia [1]
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BPH	Benign prostatic hyperplasia
CAP(s)	Centrally authorised product(s)
CAPS	Cryopyrin-associated periodic syndromes
CD	Crohn's disease
CF	Cystic fibrosis
CHMP	Committee for Medicinal Products for Human Use
CIDP	Chronic inflammatory demyelinating polyneuropathy
Classification Guideline	See Reference (2)
CMDh	Co-ordination group for Mutual recognition and Decentralised procedures – human
CML	Chronic myeloid leukaemia
COPD	Chronic obstructive pulmonary disease
CRVO	Central retinal vein occlusion
CTD	Common Technical Document
DDD	Defined daily dose
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
DP	Drug product
DPMA	Deutsches Patent- und Markenamt (German Patent and Trade Mark Office)
DRG	Diagnosis-related group
DVT	Deep vein thrombosis
EC	European Commission
EMA	European Medicines Agency
EPAR	European public assessment report
EPAR research	EPAR analysis as is explained in Section 4.1
ERA	Environmental risk assessment
EURD	European Union reference date
F2F	Face-to-face

FDA	U.S. Food and Drug Administration
G-BA	Federal Joint Committee
GCT	Giant cell tumour
HIV-1	Human immunodeficiency virus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International nonproprietary name
ITP	Primary immune thrombocytopenia
IQWiG	Institute for Quality and Efficiency in Health Care
LHON	Leber's hereditary optic neuropathy
MA(A)	Marketing authorisation (application)
MAH	Marketing authorisation holder
MCRC	Metastatic colorectal cancer
MP	Medicinal product
MRI	Mutual recognition information
MS	Multiple sclerosis
NVAF	Nonvalvular atrial fibrillation
NAP	Nationally authorised product
NAS	New active substance[1]
New API	New active pharmaceutical ingredient[2]
NIH	National Institutes of Health
ODD	Orphan medicinal product (drug) designation
OMP	Orphan medicinal product
PAH	Pulmonary arterial hypertension
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee
PE	Pulmonary embolism
PEI	Paul-Ehrlich-Institut
PK	Pharmacokinetic(s)
(P)PH(N)	(Persistent) pulmonary hypertension (of the

[1] Here: in the meaning of Annex I of Reference (3)

[2] Here: in the meaning of § 35a SGB V

	newborn)
PIP	Paediatric investigation plan
PL	Package leaflet
PPP	Purchasing power parity
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PUMA	Paediatric-use marketing authorisations
RCC	Renal cell carcinoma
RCT	Randomized controlled trial
RMP	Risk Management Plan
RoI	Return on Investment
SEGA	Subependymal giant cell astrocytoma
SGB V	Sozialgesetzbuch Fünftes Buch
SHI	Statutory health insurance
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SmPC	Summary of product characteristics
SPC	Supplementary protection certificate
STS	Soft tissue sarcoma
SVT	Superficial vein thrombosis
TPP	Target product profile
TSC	Tuberous sclerosis complex
VAR	Variation assessment report
VerfO	Verfahrensordnung (see Reference (4))

1 Introduction

The extension of an initially approved indication is one of the "four predominant methods for extending the lifecycle" of an MP in the post authorisation phase [5], [6], [7]. The other three methods are "chemical reformulation", "combination with another existing drug" and "new delivery method" [5].

Marketing considerations play an important role in the introduction of extended indications. The frequency of the indication (i.e. incidence and prevalence of the respective disease) directly determines the MP's potential sales volume. This also influences the pricing strategy. At constant fixed costs one daily dose of an MP can be calculated significantly cheaper for 100,000 patients than for 100 patients [8]. For a prominent case see Example 1.

Example 1 API: alemtuzumab

MabCampath was initially authorised on 06/07/2001 for the orphan indication B-CLL [9]. In 2012 the MAH withdrew it from the market to relaunch it in 2013 at a significantly higher price under the name Lemtrada for the indication MS. MS is "the most common cause of neurological disability in young adults worldwide" [10]. The commercially[3] motivated withdrawal of MabCampath led to controversial debate [10], [11].

The regulatory background of extensions of indications is complex, and no overarching EU guideline exists. To begin with, the extension of an indication can result from various changes, and different procedures can lead to an extended indication which follow different timing strategies. Diverse incentives may be applicable, and a wide range of regulatory aspects needs to be considered for the assessment of extensions of indications. Finally, in launching an MP with an extended indication it is also necessary to take into account market access aspects.

[3] The turnover for the MS indication is augmented not only by the increased number of patients but also by the increased treatment duration and the decreased dose of the API. [12]

The scope of this master thesis is to show the different criteria for extensions of indications (Chapter 2), to provide an overview of regulatory strategies used in introducing a new indication (Chapter 3), their relevance and timing (Chapter 4), the possible incentives (Chapter 5) and the regulatory assessment of extensions of indications (Chapter 6). The present study also serves to provide orientation on the access of reimbursable MPs with extended indications to the German market (Chapter 7). As the market access is not harmonised, national provisions need to be considered for any particular EU member state [13]. Therefore, the focus of the current study is on the German market.

This thesis aims to reach regulatory affairs employees of pharmaceutical companies holding MAs for innovator products that are authorised in the EU and that are candidates for extensions of indications. Therefore, another scope of the present study is to establish practical relevance by providing appropriate examples of the various issues.

The thesis centres on innovator CAPs for human use. The reason for this focus on CAPs is that an EPAR is available for each CAP [14]. EPARs provide comprehensive and - due to the standardised form - easily analysable up-to-date data on the assessment history of CAPs, including the assessment of extensions of indications [15], [16]. To quantify both the timing and relevance of the different procedures to introduce extensions of indications and the relevance of incentives, an EPAR research is conducted, i.e. EPARs of all 726 currently[4] approved innovator CAPs for human use are examined, as explained in Section 4.1.

[4] Status: 02/01/2016

2 Criteria for extensions of indications

In general, a new indication includes at least one of the following criteria [17], [18], [19]:

1. “A new target disease”
2. “Different stages or severity of a disease”
3. “An extended target population for the same disease, e.g. based on a different age range or other intrinsic (e.g. renal impairment) or extrinsic (e.g. concomitant product) factors”
4. “Change from the first line treatment to second line treatment (or second line to first line treatment), or from combination therapy to monotherapy, or from one combination therapy (e.g. in the area of cancer) to another combination”
5. “Change from treatment to prevention or diagnosis of a disease”
6. “Change from treatment to prevention of progression of a disease or to prevention of relapses of a disease”
7. “Change from short-term treatment to long-term maintenance therapy in chronic disease”

3 Regulatory strategies

This chapter describes the different procedures that can achieve an extended indication.

3.1 Type II variation

The most common approach used in adding a new indication is to apply for a Type II variation according to Annex II No 2a of Regulation (EC) No 1234/2008. The change to an indication refers to the variation category C.I.6.a [2]. This is a procedure of Type II, which costs € 83,700, and for which a “90-day timetable” applies [20]. The INN of the MP remains unchanged.

In the following cases a Type II variation cannot be applied to extend the indication:

- Where the indication of a non-orphan MP is extended to include an orphan indication. This scenario requires a new MAA (see Section 3.2)
- Where the strength, pharmaceutical form or route of administration of the MP is changed in parallel

In the latter case the Type II variation to extend the indication needs to be included in a *line extension*[5] by grouping [(21)]. A line extension also costs € 83,700, but here a 210-day timetable applies, i.e. the procedure takes just as long as the procedure for a new MA [(21)].

Compared to the product name of the existing MA, the INN of the MP "will be the same for the 'extension'" [(21)]. The entire name of the MP is "commonly composed of the 'invented name, followed by the strength, pharmaceutical form'" [(21)]. Therefore, the entire name of the MP may be different for the line extension in cases where the strength (see Example 2) or pharmaceutical form (see Example 3) change.

Example 2 API: lenalidomide

On 14/06/2007 Celgene Europe Ltd was granted the MA for Revlimid *5 mg* hard capsules, Revlimid *10 mg* hard capsules, Revlimid *15 mg* hard capsules and Revlimid *25 mg* hard capsules for the 2nd line treatment of multiple myeloma in combination with dexamethasone [(22)]. On 19/02/2015 the line extension was approved for Revlimid *20 mg* hard capsules for the 1st line treatment of non-transplantable multiple myeloma patients [(23)].

Example 3 API: darunavir

On 12/02/2007 Janssen-Cilag International NV was granted the MA for Prezista 300 mg *film-coated tablets* for the treatment of HIV-1 infection in adult patients [(24)]. On 24/10/2012 the line extension was approved for Prezista 100 mg/ml *oral suspension* for the treatment of HIV-1 infection in paediatric patients [(25)].

[5] Article 19 of Regulation (EC) No 1234/2008 in conjunction with Annex I

For the timing and relevance of Type II variations to extend the indication, please refer to Section 4.2.

3.2 New MAA for the new indication [21]

A further approach to achieve an extension of an indication for an API is a new MAA.

This alternative can be chosen to market the MP with the new indication under a new name, because the INN of the new MP will be different from that of the existing MP [26].

Another scope for the application for a new MA for the extended indication arises when an MP that has been authorised "for a non-orphan indication" is authorised "for another indication which is orphan", because "orphan and 'non-orphan' indications may not be covered by the same [MA]" [27]. See Example 4 and Example 5 in Section 3.2.1 for OMPs that have been authorised on the legal basis of Article 8(3). See Example 6 in Section 3.2.2 for an OMP that has been authorised on the legal basis of Article 10(3).

3.2.1 Application according to Article 8(3)

In cases where the application for the new MA does not refer to non-clinical and clinical data of a reference MP, a full set of non-clinical and clinical data needs to be presented. The legal basis for this type of new MAA is Article 8(3).

In general, the "basic fee" is € 278,800 [28], and a 210-day timetable applies[6].

MA approvals on the legal basis of Article 8(3) including extended indications are possible for both known APIs and NAS. NAS include APIs that "[differ] significantly in properties with regard to safety and efficacy from that chemical substance previously authorized" in the EU Annex I of (3). Examples for known APIs and NAS

[6] Article 6 No 3 of Regulation (EC) No 726/2004

approved on the legal basis of Article 8(3) with extended indications are listed in Table 1 and Table 2.

For examples for OMPs see Example 4 and Example 5.

Example 4 API: everolimus

On 03/08/2009 Novartis Europharm Ltd was granted the MA for Afinitor, 2.5 mg tablets for the indications "hormone-receptor-positive advanced breast cancer", "neuroendocrine tumours of pancreatic origin" and RCC [29]. About 2 years later, on 02/09/2011 the MAH was granted the conditional MA for Votubia 2.5 mg tablets for the orphan indications "renal angiomyolipoma" and SEGA, both associated with TSC [30] (see Table 1).

Example 5 API: nintedanib

On 21/11/2014 Boehringer Ingelheim International GmbH was granted the MA for Vargatef 100 mg soft capsules, which is not an OMP. About 2 months later, on 15/01/2015, the MAH was granted the MA for the OMP Ofev 100 mg soft capsules (see Table 2).

3.2.2 Application according to Article 10(3) (hybrid application)

When a new MAA refers to non-clinical or clinical data of the reference MP, and additional non-clinical or clinical data are provided to extend the indication, the legal basis for this type of new MAA is Article 10(3).

In general the "basic fee" for a hybrid application is € 108,200 [28], and a 210-day timetable applies[7].

For an example for an OMP, see Example 6.

Example 6 API: idebenone

On 08/09/2015 Santhera Pharmaceuticals Deutschland GmbH was granted the

[7] Article 6 No 3 of Regulation (EC) No 726/2004

MA for the OMP[8] Raxone, which is "indicated in patients 14 years of age and older" with LHON (31). The reference MP for Raxone is Mnesis 45 mg tablets, that was "authorised in Italy" in 1993 for the "treatment of cognitive and behavioural deficits" due to specific "cerebral pathologies" (31) (see Table 3).

4 Timing and relevance of extensions of indication

4.1 EPAR research

For the EPAR research, the EPARs of all 726 currently[9] approved innovator CAPs for human use are analysed. Generic CAPs or biosimilars are not considered.

Quantifying extensions of indications that result from Type II variations requires consultation of the EPAR component "tabulated overview of procedural steps taken before and after authorisation". The relevant search terms are "extension of indication" or "C.I.6.a", where the latter stands for the variation category in the Classification Guideline (2).

For identifying the subset of extensions of indications that are embedded in line extensions the relevant search terms are "line extension" or "X" as part of the application number. For details on the assessment, the respective VARs are consulted.

To identify new indications that are introduced with a new MA on the legal basis of Article 8(3) and Article 10(3), all MPs that are authorised on the legal basis of Article 8(3) and Article 10(3) are selected. This is done by means of the corresponding "Public assessment report for the initial authorisation" (15), chapter "Background information on the procedure". As indicator for a new indication that is introduced with a new MA on the legal basis of Article 8(3), an indication specific EURD[10] is taken. This is the case when different EURDs exist for different

[8] ODD no.: EU/3/07/434, dated 15/02/2007

[9] Status: 02/01/2016

[10] The EURD "corresponds to the date of the first or the earliest known date" of the MA in the EU of an MP containing the API or combination of APIs. (32)

indications of the same API. To identify new indications that are introduced with a new MA on the legal basis of Article 10(3), the respective "Public assessment report for the initial authorisation" (15) is consulted, which provides differences compared to the reference MP, e.g. a new therapeutic indication.

4.2 Extensions of indication resulting from Type II variations

Following the EPAR research (see Section 4.1), the number of extensions of indication has been calculated for each MP. Investigating the timing of the extension of indication involves the investigation of the period between the submission of the variation application and the submission of the initial MAA. The submission date of the initial MAA is taken from the corresponding initial EPAR. The submission date of the variation application is taken from the corresponding VAR. If no such submission date is given in the VAR, the submission date is estimated by subtracting 90 days from the issue date of the CHMP opinion[11]. For the 90-day timetable, please refer to Section 3.1.

The results for the timing analysis are shown in Figure 1[12].

[11] This issue date is stated in the EPAR, part "Procedural steps taken and scientific information after authorization".

[12] As this is not deemed relevant for the timing of extensions of indications, no distinction is made between Type II variations that are included in line extensions by grouping and Type II variations that are not grouped (see Section 3.1).

Figure 1: Timing of submissions of Type II variations to extend the indication after the submission of the initial MAA

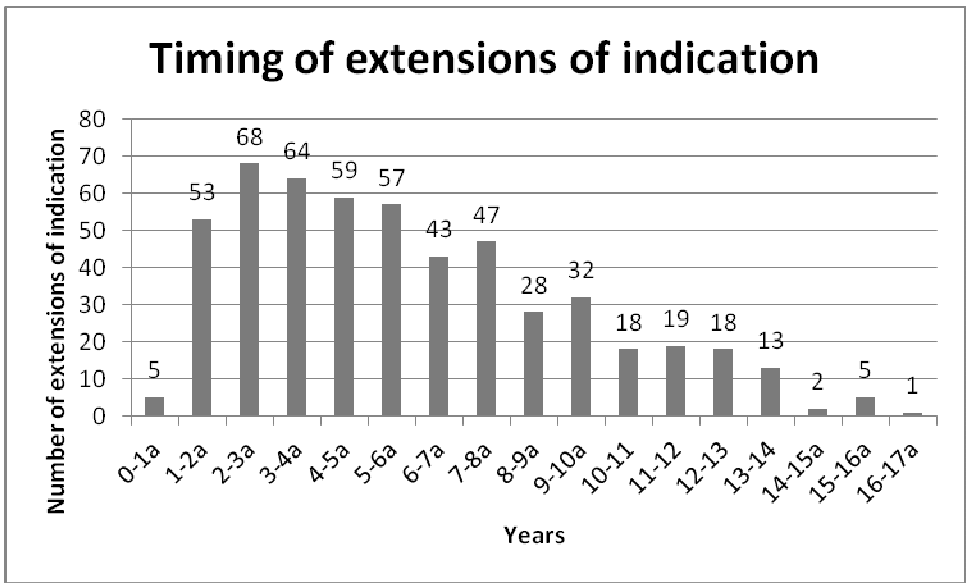

Figure 1 shows a maximum of the frequency distribution of submissions of indication extensions at 2-3 years after the submission of the initial MAA. Afterwards, the number of submissions of variation applications to extend the indication decreases continuously.

This can be explained by the fact that the earlier the new indication is submitted and approved the more time remains for profiting from the extended indication. This is because the period of market exclusivity of the MP, i.e. the period that remains until generics or biosimilars may be launched, is limited.

In general, the timing is not as critical for biologic MPs as it is for “chemically-derived” MPs, because the requirements for the MAA of biosimilars are more stringent than those for the MAA of generics [(33)]. Given the complexity of biologic APIs, the “demonstration of bioequivalence” is “not sufficient to demonstrate similarity” with the biological reference MP [(33)]. Rather it is the comparability, e.g. as regards “safety and efficacy”, which needs to be comprehensively demonstrated [(33)].

For an overview of the number of procedures for MAAs for biosimilars, please refer to Table 4.

Commonly, the marketing protection period expires not later than 10 years after the submission of the initial MA. For PIP compliant OMPs 12 years of marketing protections apply instead (see Example 7). For details on the different protection periods, please refer to Reference (34), Sections 2.4.1 and 2.4.3.

Example 7 API: anagrelide

For the OMP Xagrid, which was authorised on 16/11/2004 under exceptional circumstances (submission date of initial MA: 26/03/2002), an extension of indication was submitted on 07/02/2014 based on a completed PIP, i.e. almost 12 years after the submission of the initial MA.

Even though 12 years had elapsed before the submission of the initial MAA, extensions of indications were submitted. As long as a patent or SPC is valid, extensions of indications may be profitable. The SPC[13] expires not later than 15 years[14] +6 months[15] after the initial MA. To date, extensions of indications have been submitted for up to 17 years after submission of the initial MAA (see Figure 1).

In the cases shown in Table 5, the extensions of indications were submitted more than 15 years after the submission of the initial MAA.

At the point in time of the submission of the latest Type II variations to extend the indication of some of the MPs listed in Table 5, the following specific conditions might have supported the decision to extend the indication:

- In the case of Sustiva a formulation patent was still valid (35), (36)
- In the case of BeneFIX, Enbrel and MabThera, the API is biological, and no biosimilar has been authorised in the EU
- In the case of Enbrel additional 6 months of SPC apply (see Section 5.5)
- In the case of Rebetol the extension of indication was recommended by the PRAC in a “PSUR assessment” (37)

[13] For details on the SPC, please refer to Reference (34), Section 3.2.2.

[14] Recital 9 in conjunction with Article 13 No 1 of Regulation (EC) No 469/2009

[15] For the 6 months, please refer to Section 5.5.

The results of the analysis of the relevance of Type II variations to extend the indication are shown in Figure 2.

Figure 2: Relevance of Type II variations to extend the indication - in detail

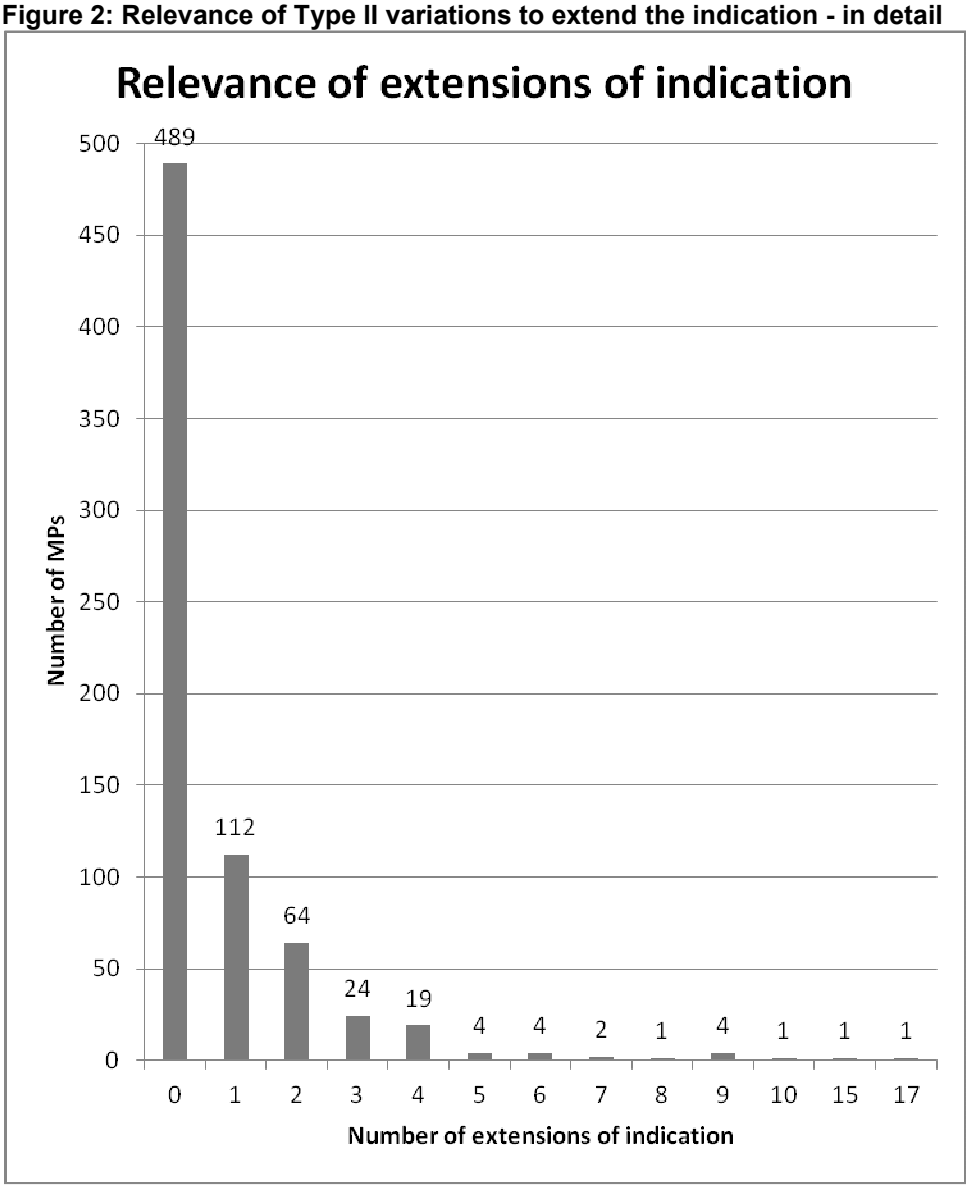

Figure 2 shows the frequency distribution of the number of indication extensions. This frequency distribution can be divided into the following three partitions: 67%, i.e. about two-thirds of the MPs analysed were not subject to any Type II variation procedure to extend the indication. For 30% one to four Type II variation procedures resulted in the extension of an indication. For 2-3% five or more Type II variation procedures resulted in the extension of an indication (see Figure 3).

Figure 3: Relevance of Type II variations to extend the indication - summary

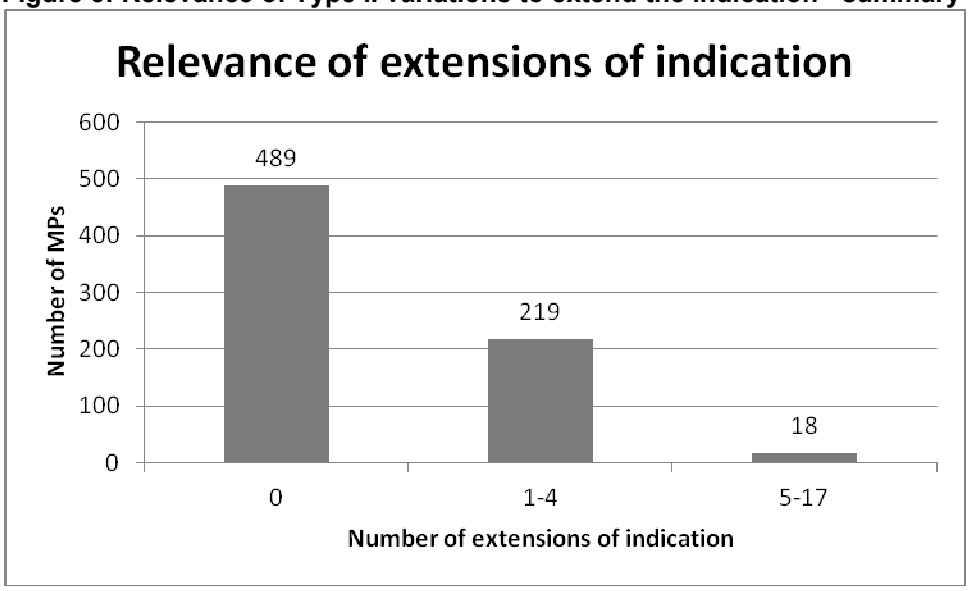

Figure 2 and Figure 3 do not distinguish between Type II variations that are not grouped and Type II variations that are included in line extensions by grouping (see Section 3.1). However, the subset of Type II variations to extend the indication that are embedded in line extensions is identified within the EPAR research (see Section 4.1), and a total of ten MPs were found for this approach (see Table 6).

4.3 New MA according to Article 8(3)

The EPAR research (see Section 4.1) found 349 MAs approved on the legal basis of Article 8(3). The subset of MPs subject to an extended indication are identified on the basis of an indication specific EURD. The identified MPs are shown in Table 1 and Table 2. In 10 cases, the legal basis of the MA refers to a known API (see Example 8 and Table 1). In five cases, the legal basis of the MA refers to an NAS (see Table 2).

This does not mean that all cases of MPs that have been authorised on the legal basis of Article 8(3) are automatically ruled out from being subject to extensions of indications where the EURD of the API is not indication specific. Indeed there is a certain level of uncertainty here, as in the following cases:

- Thirty-seven cases of MPs that have been authorised on the legal basis of Article 8(3) for a *known* API
- Nineteen cases of MPs that have been authorised on the legal basis of Article 8(3) where no information on the API (NAS vs. known API) is provided in the EPAR, but where the EURD is older than the MA date

Only a case-by-case evaluation could determine whether the indication authorised for the above named MPs is different to the indication of another CAP or NAP containing the same API that has been authorised in the EU in the past. Conducting a case-by-case evaluation will not be pursued in this master thesis, however.

For the timing of extensions of indication submitted on the legal basis of Article 8(3) considerations about data or market protection periods are not relevant, because these applications do not refer to pre-clinical or clinical data of a reference MP and therefore trigger fresh data and market protection periods (see Section 6.1.6 of Reference (3)). Please also refer to Section 5.5.

Example 8 known API: collagenase Clostridium histolyticum

The MP Xiapex was authorised on the legal basis of Article 8(3) on 28/02/2011 for the treatment of Dupuytren's contracture and treatment of Peyronie's disease. The EURD for this indication is identical to the MA date of Xiapex. For collagenase Clostridium histolyticum another EURD, dated 12/12/1969, exists which refers to all other indications.

4.4 Hybrid application according to Article 10(3)

The EPAR research (see Section 4.1) found 16 different[16] hybrid applications.

[16] The hybrid applications for Budesonide / Formoterol Teva, Budesonide / Formoterol Teva Pharma B.V. and Vylaer Spiromax refer to the same API and have the same MA date - therefore, they are summarised. This also applies for the hybrid applications for BiResp Spiromax and DuoResp Spiromax.

Seven[17] of these 16 hybrid applications include a change in the therapeutic indication compared with the reference MP (see Table 3).

MPs that are authorised on the legal basis of a hybrid application can only be marketed after the expiration of the market protection period of the reference MP (3). This could explain why extensions of indications on the legal basis of a hybrid application are rare.

5 Incentives for extensions of indication

The community legislation foresees different incentives for extensions of indications (7), which are outlined in this chapter. The chapter explores the relevance of the different incentives that may apply for extensions of indications, and provides examples. The legal framework is explained in Reference (34).

5.1 "One year of data exclusivity for a new indication" for "well established substances" according to Article 10(5) of Directive 2001/83/EC (18)

When a "new indication" is applied for a "well-established substance", a "non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication" [18].

For the explanation of a "well established substance", please refer to Reference (34), Section 2.3.1 [19].

Theoretically, a "new indication submitted after 20/11/2005 may benefit from this year of protection" (39) which refers to the "study data only" (7). A positive outcome

[17] The extensions of indication for Controloc Control, Pantecta Control, Pantoloc Control, Pantozol Control and Somac Control are identical. Therefore, they are summarised.

[18] Article 10(5) of Directive 2001/83/EC

[19] Please note, that the definition "well established substance" does not depend on the "legal basis of the well established use procedure". (39)

for the assessment of the requested year of data protection should be published for CAPs in Annex IV of the EPAR [40]. The following wording is specified: "The CHMP reviewed the data submitted by the [MAH], taking into account the provisions of Article 10(5) of Directive 2001/83/EC, and considers that <the <pre-clinical tests> <and> <clinical studies> carried out in relation to the new indication were significant as further explained in the [EPAR]" [41].

In practice, no publication of the acceptance of such extended data exclusivity is found within the EPAR research (see Section 4.1) [20].

5.2 Additional "one year of market protection for a new indication" with "significant clinical benefit" according to Article 14(11) of Regulation (EC) No 726/2004

The legal basis for an additional one year of market exclusivity for extensions of indication is Article 14(11)[21] of Regulation (EC) No 726/2004 for CAPs [17]. This legal basis is applicable for "initial MAA submitted after" 20/11/2005 [7].

The marketing protection period is "extended to a maximum of 11 years" if a new indication which is "held to bring a significant clinical benefit in comparison with existing therapies" is authorised "during the first eight years" of the regular marketing protection period of ten years [22]. The "significant clinical benefit" can stem from improved efficacy or safety, from "major contribution to patient care" or from a lack of any existing therapy [7]. If the MAH "wishes to claim (additional) data/market exclusivity when applying for a new indication" this needs to be included in CTD Module 1.5.3 [43].

A positive outcome of the assessment of the requested additional year of market protection is published for CAPs in Annex IV of the EPAR. The wording is specified as follows [40]: "The CHMP reviewed the data submitted by the [MAH],

[20] In comparison, two cases are published where such extended data exclusivity was accepted for *nationally* authorised MPs. [42]

[21] For NAPs Article 10(1) of Directive 2001/83/EC applies instead.

[22] Article 14(11) of Regulation (EC) No 726/2004

taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with [the] existing [therapeutic indication] as further explained in the [EPAR]" [41].

Publications of the acceptance of such extended data exclusivity were found for 18 CAPs (see Table 7) within the EPAR research (see Section 4.1).

5.3 PUMA

For the explanation of incentives for PUMAs, please refer to Reference (34), Section 2.4.2.

The eligibility for a PUMA refers to MPs "developed specifically for children that are already authorised but are not protected by a patent or [SPC]" [44].

Currently two PUMAs have been approved (see Table 8) [45], [46].

5.4 Extended market exclusivity for orphan indications

For the explanation of incentives for orphan drugs, please refer to Reference (34), Section 2.4.3.

When the indication of OMPs is extended and the new orphan indication[23] receives a separate ODD, an extended market exclusivity applies. However, one MA can include several ODDs, and each ODD "triggers its own [10 years] market exclusivity period kicking-off from [the] start of approval of the indication" [7].

Examples are Imbruvica, Nexavar and Revlimid (see Table 9). Please also refer to Section 6.3.

[23] i.e. an indication either referring to a "life-threatening or chronically debilitating condition" that affects ≤ 0.05 % of the EU population or referring to a "life-threatening, seriously debilitating or serious and chronic condition" with a negative RoI (Article 3(1)(a) of Regulation (EC) No 141/2000)

5.5 Incentives referring to patents and additional six months SPC

In principle, for extensions of indication that are introduced with a new MA on the legal basis of Article 8(3), an off-patent[24] API can be covered by a patent for the new indication (47). This is not elaborated in this master thesis in more detail, because this is a matter of patent affairs.

For an explanation of the incentive to extend the SPC by 6 months, please refer to Reference (34), Section 2.4.2. Essentially, the SPC can be extended "by six months", where results of PIP compliant studies are "included in the product information", even in the case of negative "studies' results" (7). This means that there is no direct link between this incentive and the authorisation of the extension of the indication to include a paediatric indication. Therefore, this incentive is not elaborated in more detail.

Nevertheless, 22 CAPs with an extended SPC have been identified (see Table 10).

6 Regulatory assessment/Dossier requirements

Introducing extensions of indications with a new MAA requires the presentation of a complete dossier. For extensions of indications that are introduced with a new MA on the legal basis of Article 8(3) this is a stand-alone dossier, and for extensions of indications that are introduced with a new MA on the legal basis of Article 10(3) the dossier relies "in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data" (3).

This chapter presents the dossier requirements for Type II variations to extend the indication. In general, when extending the indication for an MP via a Type II variation "supporting data" need to be provided (48), and several chapters of the dossier need to be updated.

[24] Please also refer to Reference (34), Section 3.3, 2nd sentence.

6.1 Update of the SmPC and PL & user consultation (CTD Module 1.3)

The revised product information that is affected by the variation, i.e. SmPC and PL needs to be submitted. The presentation must be "in accordance with the appropriate headings and numbering of the EU-CTD format" Section 2.3.1 of (48).

Certainly, the following chapters require updating at the very least:

- SmPC Chapter 4. "Clinical particulars", especially Chapter 4.1 "Therapeutic indication"
- PL Chapter 1. "What X is and what it is used for"

Other chapters need to be updated where applicable. E.g. in the case of an extension application SmPC Section 4.2 "Posology and method of administration" and PL Chapter 3. "How to <take> <use>" will need to be updated if the route of administration is changed simultaneously. In the case of relevant new "findings in the non-clinical testing", the Section 5.3 "Preclinical safety data" of the SmPC must be updated accordingly (19).

User consultation is required to check if the PL is readable and useful for "target patient groups" when "significant changes are made". The user consultation "should be part of Module 1 of the application dossier"[25] (49), (50).

In general, a "full user test" (51) is required to "show that the [PL] meets the criteria for readability" (52), (53). Examples where the user test results were submitted with a Type II variation application to extend the indication are Soliris (52) and Votubia (53). One example where the submitted results were not accepted, and where an "additional reduced readability test" was requested is Ilaris (54).

In the case of Afinitor (55) and Sustiva (56) a "justification for not performing a full user consultation" was submitted. In the case of Afinitor this was accepted by the CHMP, because the "changes to the [PL] were considered minor with no

[25] Article 59(3) of Directive 2001/83/EC

consequential impact on the readability of the [PL]" [55]. By contrast, in the case of Sustiva the CHMP did not accept the justification and requested a user consultation.

In place of a "full user test" it is possible to perform a "focus test" which concentrates on a "new method or route of administration" when an MP "includes a new method or route of administration but is otherwise identical to an existing presentation" [51], [57]. In the case of Eylea, where the indication was extended to include the CRVO indication in the "prefilled syringe and vial presentations" a "focussed testing report" was requested [58].

Another alternative to a "full user test" is "bridging", which applies when the results of a user consultation can be extrapolated to "another leaflet" which is "sufficiently similar in both content and layout" [51], [57]. In the case of Eylea, a "bridging report" that referenced to "Eylea 40 mg/ml solution for injection in a vial (as submitted and endorsed with the previous extension of indication application for CRVO)" was presented [59].

6.2 ERA (CTD Module 1.6)

Since 01/12/2006, the "evaluation of the environmental impact should be made [for Type II variations] if there is an increase in the environmental exposure", i.e. if a new indication results "in a significant increase in the extent of the use" [60]. A "justification for not submitting ERA studies" may be presented instead, e.g. for proteins, vaccines and other substances as API which are "unlikely to result in a significant risk to the environment" [60]. See Examples 9, 10 and 11 as cases of different ERA outcomes.

Example 9 API: darunavir

In the case of Prezista, the "CHMP agreed with the MAH that no increase in the environmental exposure was expected" due to the new indication and therefore accepted that no ERA update was submitted [61].

Example 10 API: ibrutinib

In the case of Imbruvica, the "total consumption of [the API] ibrutinib on the EU market within the approved indications […] and the intended indication […] has been recalculated". In consequence, the ERA was updated, considering the "estimated consumption volume of 9200 kg/year in the year 2021" for the API [62].

Example 11 API: methylnaltrexone bromide

In the case of Relistor, the CHMP concluded that the "new indication leads to a clear increase in the number of patients treated" and that a "risk of methylnaltrexone bromide to the environment" cannot be excluded and recommended the submission of a Phase II ERA, i.e. an "environmental fate and effects analysis" [60], [63].

6.3 Orphan Drugs (CTD Module 1.7)

"Orphan and 'non-orphan' indications may not be covered by the same [MA]" (see Section 3.2) [27]. This means that when the indication of an OMP is extended, two cases can be distinguished:

- The new indication receives a separate ODD. Examples are Imbruvica and Nexavar (see Table 9)
- The new indication is covered by the existing ODD. Examples are Arzerra, Firazyr, Kalydeco, Kuvan, Soliris, Votubia, Xagrid (see Table 9)

The EPAR research (see Section 4.1) identified 18 OMPs with a Type II variation to extend the indication (see Table 9).

In cases where the new indication is identical to an existing orphan indication the MP may not be similar to the existing OMP because of its market exclusivity[26]. Please also refer to Section 2.4.3 of Reference (34). An OMP is similar to another OMP when the API is identical or when the API has "the same principal molecular structural features" and "acts via the same mechanism" [27].

[26] Article 8 No 1 of Regulation (EC) No 141/2000

[27] Article 3 No 3 of Regulation (EC) No 847/2000

In the case of Sprycel [64] and Revatio [65], [66], for example, the MAH could prove non-similarity. Whereas in the case of Tasigna the CHMP considered similarity "to Glivec for the same therapeutic indication. However, the [MAH] for Glivec has given his consent to the MAH" [67] (see Table 9).

6.4 Pharmacovigilance (CTD Module 1.8)

6.4.1 PSUR cycle

A new indication that is "broadening the exposed patient population" might be a criterion for the CHMP to decide - "after consultation with the PRAC" - to shorten the "frequency of submission of PSURs" that is defined in Article 107c(2)(b) of Directive 2001/83/EC (see Example 12) Section VII.C.3.4 of [68].

Example 12 API: collagenase Clostridium histolyticum

In the case of Xiapex (MA date: 28/02/2011), an application for a new indication was submitted on 12/06/2014 and approved on 30/01/2015. The CHMP concluded that the "frequency of PSUR submission should be revised to 6 months" [69], which shortens the PSUR cycle for the 3rd and 4th year after the MP "has been placed on the market"[28] by 6 months.

6.4.2 Additional monitoring and signal management

The assessment of an extension of an indication can result in the "decision to include" an MP in the "list of medicines under additional monitoring" [70], i.e. to label the MP with the "inverted equilateral black triangle" that is defined in the implementing Regulation (EU) No 198/2013 Section X.C.5 of [71]. For MPs that are "subject to additional monitoring" a "2-week frequency" applies for "reviewing the statistical outputs" [72]. This "2-week frequency" may also apply when the MA has been "significantly varied", e.g. by amending a new indication which modifies the "exposed patient population or the safety profile" [72] (see Examples 13 and 14).

[28] Article 107c(2)(b) of Directive 2001/83/EC

Example 13 NAS: imatinib

In the case of Glivec (MA date: 07/11/2001), an application for a new indication was approved on 28/11/2006. Additional monitoring was suggested given that "there was one case of cardiac adverse event [...] related with imatinib" (73).

Example 14 known API: everolimus

In the case of Votubia (conditional MA date: 02/09/2011), an application for a new (orphan) indication was approved on 31/10/2012. As the "potential of everolimus to affect male fertility is a concern" and "given that most patients" that fall under the new indication are of "reproductive age, the risk of everolimus affecting male fertility will be subject to additional monitoring" (74).

6.4.3 RMP (CTD Module 1.8.2)

An RMP should be updated[29] and submitted with a Type II variation to extend the indication whenever the "change to an existing" indication is significant Section V.C.3. of (75). This is the case when the "new treatment target population differs materially", e.g. in the case of a:

- "new disease area",
- "new age group (e.g. paediatric indication)",
- "move from severe disease to a less severely affected population",
- "move from 2nd line or other therapy" or
- "change to the concomitant medication" for an oncologic MP Section V.C.3. of (75)

The "format and content" of the RMP is set out in law.[30]

6.5 PIP (CTD Module 1.10)

Since 26/01/2009[31], Article 7 of Regulation (EC) No 1901/2006 requires consideration for extensions of indication that are submitted via a Type II variation

[29] E.g. with regard to module "epidemiology of the indications and target population" (75)(75) Section V.B.8.1

[30] Articles 29 to 38 of the implementing Regulation (EU) No 520/2012

or with a new MAA on the legal basis of Article 8(3). Article 7 does not affect hybrid applications or off-patent MPs[32] (21).

The following needs to be submitted with the application to extend the indication[33]:

- "results of all studies performed […] in compliance with an agreed [PIP]" (see Example 15) or a
- "product-specific waiver" (see Example 16) or a
- "class waiver" (see Example 17) or a
- deferral decision (see Example 18)

Please also refer to Reference (34), Section 2.3.3.

"Both the existing and the new indications" need to be covered by the documents required, "irrespective of whether the change is related to adult or paediatric use" (21).

Example 15 NAS: meningococcal Groups A, C, W-135 and Y conjugate vaccine

In the case of Menveo (MA date: 15/03/2010), an application for a Type II variation was submitted on 08/08/2011 to extend the indication, and "at the time of submission of the application, the PIP […] was completed. The PDCO issued an opinion on *compliance for the PIP*" (76).

Example 16 NAS: canakinumab

In the case of Ilaris (date of MA approval under exceptional circumstances: 23/10/2009), an application for a Type II variation was submitted on 07/11/2012 to extend the indication, and the "application included […] the granting of a *(product-specific) waiver* in children from birth to less than 24 months" (54).

Example 17 NAS: panitumumab

In the case of Vectibix (conditional MA date: 03/12/2007), an application for a

[31] Article 57(2) of Regulation 1901/2006

[32] Article 8 of Regulation (EC) No 1901/2006

[33] Article 7 of Regulation (EC) No 1901/2006

Type II variation was submitted on 04/11/2014 to extend the indication, and the "application included an EMA Decision CW/1/2011 on the granting of a *class waiver*" (77).

Example 18 NAS: dabigatran etexilate

In the case of Pradaxa (MA date: 18/03/2008), an application for a Type II variation was submitted on 03/06/2013 to extend the indication. "At the time of submission [...] the PIP was not yet completed as some measures were *deferred*" (78).

6.6 Quality (CTD Modules 2.3 and 3)

Apart from presenting the supporting quality data "relating to the proposed" variation as part of Module 3, the quality overall summary (CTD Module 2.3) needs to be updated or amended, "as relevant" Section 2.3.1 of (48).

6.6.1 Changes to strength, pharmaceutical form and route of administration

Extensions of indications are subject to a line extension procedure when changes to strength, pharmaceutical form and route of administration apply (see Section 3.1).

Changes to strength, pharmaceutical form or route of administration include[34]:

- "change of bioavailability"
- "change of pharmacokinetics e.g. change in rate of release"
- "change or addition of a new strength/potency" (see Example 19)
- "change or addition of a new pharmaceutical form" (see Example 20)
- "change or addition of a new route of administration"

Example 19 API: anakinra

In the case of Kineret (MA date: 08/03/2002), an application "for a new indication in adult and paediatric patients for the treatment of [...] CAPS" and for a "*new*

[34] Annex I No 2 of Regulation (EC) No 1234/2008

strength 100 mg / 0.67 ml solution for injection in a pre-filled syringe" was included within the line extension that was submitted on 30/10/2012 (79).

Example 20 API: raltegravir

In the case of Isentress (MA date: 20/12/2007), an extension of the indication to include a paediatric HIV-1 indication and an application for "chewable tablets" as a "*new pharmaceutical form*" was included within the line extension that was submitted on 04/07/2011 (80).

6.6.2 Other consequential quality changes grouped with extensions of indications

Other changes can be grouped with a variation to extend an indication as long as these changes are "consequential to this major variation of Type II"[35].

One possibility could be up scaling. Theoretically, the introduction of a new indication is expected to result in an increased demand for the MP – depending on the incidence and prevalence of the new indication. It is not only in the interest of the MAH, indeed the MAH is also obliged to "ensure appropriate and continued supplies of that [MP] [...] so that the needs of patients [...] are covered"[36] in order to avoid shortages of the MP. Therefore, in certain cases the up scaling of the manufacturing process to increase the batch size may be necessary (see Example 21).

Example 21 NAS: dabigatran etexilate

In the case of Pradaxa (MA date: 18/03/2008,) an application for a line extension was submitted on 05/01/2010 to add "a new strength: 150 mg" and to "include a new indication", i.e. "prevention of stroke and systemic embolism in adult patients with atrial fibrillation". This line extension was grouped with several quality changes, including a variation of Type IB (Class: B.II.b.4) concerning the increase of the batch size of the DP "due to introduction of 2nd gen[eration] DP

[35] Annex III No 2 of Regulation (EC) No 1234/2008

[36] Article 81(2) of Directive 2001/83/EC

manufacturing process" [81].

Examples for other groupings are presented in Table 11.

6.7 Pre-clinics and Clinics

6.7.1 Pre-clinics (CTD Modules 2.4, 2.6 and 4)

The non-clinical overview (CTD Module 2.4) and non-clinical summary (CTD Module 2.6) need to be updated or amended "as relevant" when non-clinical "study reports are submitted" as part of Module 4 Section 2.3.1 of [48].

When the extension of the indication is related to a "new target disease" (Criterion No. 1 according to Chapter 2) primary PD studies, i.e. "studies on the mode of action and/or effects of a substance in relation to its desired therapeutic target" may be necessary [82]. For examples, please refer to Section 6.7.3.1.

When the extension of the indication is related to an "extended target population for the same disease" (Criterion No. 3 according to Chapter 2) and the indication is extended to include paediatric patients the "strategy for the non-clinical development [...] to support paediatric use" is part of the PIP [83]. In general "clinical safety data from adult humans" are considered to be the "most relevant information" in support of the authorisation of the paediatric indication [84]. "Juvenile animal toxicity studies" should only be conducted when "non-clinical safety data from adult animals" [84] and "human safety data [...] are judged to be insufficient" Chapter 12 of [85]. This may apply in the case of concerns relating to, e.g.:

- low "safety margins" [86]
- the "mechanism of action" [86]
- when "any of the major functional [developing] systems are shown to be potential targets" [86]
- results from "pre- and postnatal development studies" [86]
- "exposure gap[s]" [84]
- results from an MP "of similar chemical structure and/or of the same pharmacological class" [86]

For examples, please refer to Section 6.7.3.3.1.

Where the extension of the target population refers to the inclusion of populations other than paediatric patients the pre-clinical requirements cannot be generalised and need to be considered on a case-by-case basis. For examples, please refer to Section 6.7.3.3.2.

Where the extension of an indication refers to the change from combination therapy to monotherapy, or from one combination therapy to another combination Chapter 17 of (85) (Criterion No. 4 according to Chapter 2) and when the extension of an indication results in the change of the recommendations given in the product information "for co-use with a specific drug, even if not in a fixed combination", the following generally applies to support the marketing of the extended indication (85):

- "Combination toxicity studies" are not recommended where there is "adequate clinical experience with co-administration", provided there is no "significant toxicological concern"[37]
- "Combination toxicity studies" are recommended where "there is not adequate clinical experience with co-administration" (85)

In the latter case the "combination nonclinical studies should generally be limited to a single relevant species", and the duration should be equivalent to the "duration of the intended clinical use" but not longer than 90 days. In addition, "combination genotoxicity, safety pharmacology, or carcinogenicity studies" are not required providing the "individual agents have been tested according to current standards" (85).

For examples, please refer to Section 6.7.3.4.1.

[37] In the case of "significant toxicological concern (e.g. similar target organ toxicity) […] this concern would be modified depending on the margins of safety and the ability to monitor the adverse effects in humans". (85) Chapter 17

Where the extension of an indication refers to the change from short-term treatment to long-term maintenance therapy in chronic disease (Criterion No. 7 according to Chapter 2), carcinogenicity studies and repeated-dose toxicity studies may be required. “Carcinogenicity studies are generally needed” when the extended indication includes a change of the treatment from short-term, i.e. “infrequently or for short duration of exposure“ to long-term, i.e. continuously or “repeatedly in an intermittent manner” (87). This applies when the indication is extended to include “chronic or recurrent conditions”[38], except for oncologic MPs “intended to treat patients with advanced cancer” (88). For examples, please refer to Sprycel and Pradaxa in Section 6.7.3.6.

In addition, the recommended “durations of repeated-dose toxicity studies to support” the new indication need to be considered when the duration of the indicated treatment is increased from ≤ 2 weeks to > 1 month and the repeated-dose toxicity studies only cover a duration of 1 month rather than 3 months, or when the duration of the indicated treatment is increased from ≤ 1 month to > 3 months and the repeated-dose toxicity studies only cover a duration of 3 instead of 6 months (85).

For an example, please refer to Arixtra in Section 6.7.3.6.

Although it is generally not expected, it is important to consider on a case by case basis whether or not additional pre-clinical data are required when the extension of an indication is based on one or more of the following criteria:

- Criterion No. 2: “different stages or severity of a disease” (see example Humira in Section 6.7.3.2)
- Criterion No. 4, part “change from the first line treatment to second line treatment” (or vice versa) (see example Halaven in Section 6.7.3.4.2)
- Criterion Nos. 5 and 6: “change from treatment to prevention[39] or diagnosis of a disease” (see example Xgeva in Section 6.7.3.5)

[38] E.g. “allergic rhinitis, depression, and anxiety”

[39] Including prevention of progression/relapses of a disease

Pre-clinical requirements for line extensions where an extension of the indication is grouped with changes to strength, pharmaceutical form and route of administration that may include a “change of bioavailability” or a “change of pharmacokinetics e.g. change in rate of release” are not considered in this chapter. Please also refer to Section 6.6.1.

6.7.2 Clinics (CTD Modules 2.5, 2.7 and 5)

The clinical overview (CTD Module 2.5) and clinical summary (CTD Module 2.7) need to be updated or amended “as relevant” when “clinical study reports are submitted” as part of Module 5 Section 2.3.1 of (48).

From a regulatory point of view the “minimum requirement” is “one controlled [Phase III] study” that confirms the “findings obtained so far in pre-clinical studies, tolerance studies, dose-finding and other Phase II studies” to support the new indication (89).

The Phase III data need to be valid, clinically relevant, statistically significant, “of good quality” and internally consistent. These data need to result from “a sufficient number of patients, with a sufficient variety of symptoms and disease conditions, collected by a sufficient number of investigators, demonstrating a positive benefit/risk in the intended population at the intended dose and manner of use” (89).

In addition, consideration must be given to clinical requirements that are raised by HTA bodies for the market access. To gain the highest possible reimbursement price in Germany the additional benefit needs to be proven (see Chapter 7). Different “levels of evidence” (90) are defined for clinical studies and, the higher the level of evidence, the higher the level of probability of the additional benefit (90).

RCTs have the highest level of evidence[40]. Priority is given to double-blind F2F[41] RCTs[42].

[40] § 5(6) AM-NutzenV

For examples of extensions of indications based on the different criterions named in Chapter 2, please refer to Section 6.7.3.

6.7.3 Examples

6.7.3.1 New target disease (Criterion No. 1)

Example 22 NAS: tadalafil

In the case of Cialis, which was approved on 12/11/2002 for the "treatment of erectile dysfunction", a Type II variation was submitted in September 2011 to introduce a new indication for the "treatment of the signs and symptoms of [...] BPH [...]".

The new indication is supported by in *vitro* PD studies in "animal and human arteries" and by in *vivo* PD studies in "rat model of genitourinary tract hypoxia" (92).

From a clinical point of view the new indication was supported by four Phase III "randomised, double-blind, placebo-controlled, 12-week, parallel-design, multinational studies performed to evaluate the efficacy and safety" of the API for the new indication (EudraCT no.: 2006-001958-27, 2008-002841-21, 2008-004337-25 and 2009-010739-42 (91)) (92).

The extension of the indication was approved on 24/10/2012 (38).

Cialis is not subject to the benefit assessment in Germany because the API is not new (see Section 7.1).

Example 23 API: human fibrinogen/human thrombin

In the case of Evicel, approved on 06/10/2008 for the "improvement of haemostasis and as suture support for haemostasis in vascular surgery", a Type

[41] i.e. studies conducted to compare the benefit of the MP against the benefit of its appropriate comparator

[42] § 5(5) VerfO

II variation was submitted on 03/10/2012 for the use of “suture line sealing in dura mater closure”.

To support the new indication an “additional pharmacology study” on “dural sealing efficacy in a canine sealing model” was submitted [93].

From a clinical point of view, the new indication was supported by a new single-blind Phase III “randomized, controlled study to evaluate the safety and effectiveness” (EudraCT no.: 2009-016501-41 [91]) of the API for the new indication [93].

The extension of the indication was approved on 26/07/2013 [38].

Evicel is not subject to the benefit assessment in Germany because the API is not new (see Section 7.1).

Example 24 NAS: human normal immunoglobulin

In the case of Privigen, approved on 25/04/2008 for the immunomodulation in ITP, “Guillain-Barré syndrome” and “Kawasaki disease”, a Type II variation was submitted on 31/05/2012 to include the immunomodulation in CIDP.

No new PD studies were submitted for the new indication. An extrapolation from “findings from research on the IVIG [intravenous immunoglobulin] mode of action” to Privigen in the new indication supported the application instead [94].

From a clinical point of view, the new indication was supported by a “prospective, multicenter, open-label” Phase III “single-arm study to demonstrate the efficacy and safety” of the API in the treatment of the new indication (EudraCT no.: 2009-017672-24 [91]) [94].

The extension of the indication was approved on 26/03/2013 [38].

Privigen is not subject to the benefit assessment in Germany because the API is not new (see Section 7.1).

For two further examples, please refer to Table 12.

6.7.3.2 Different stages or severity of a disease (Criterion No. 2)

Example 25 NAS: adalimumab

Humira was approved on 08/09/2003 for the “treatment of moderate to severe, active rheumatoid arthritis in adult patients”. Since the initial MA approval, 17 Type II variations to extend the indication have been submitted and approved. On 23/08/2012 Humira was approved for the “treatment of *moderately to severely* active” CD, which extends the indication “treatment of *severe*, active” CD by including “patients with *moderately* active” CD.

In this case, no additional pre-clinical data were submitted [96].

The new indication was supported by a re-analysis of four clinical studies in “subgroups of patients with moderately or severely active disease”. The following studies of the API in subjects with CD were re-analysed:

- A Phase II study (Identifier: NCT00055523 [95])
- Three Phase III “multi-centre randomized, double-blind, placebo-controlled” studies (Identifiers: NCT00077779, NCT00105300A and NCT00348283 [95]) [96]

These clinical studies had been “assessed by the CHMP” within “previous Type II applications” and were re-analysed for the new indication to “assess the efficacy” and “demonstrate that the safety profile” of the API is “similar when comparing patients with moderate CD or severe CD to that of placebo” [96].

Humira is not subject to the benefit assessment in Germany, because the API is not new (see Section 7.1).

6.7.3.3 Extended target population for the same disease (Criterion No. 3)

6.7.3.3.1 Paediatric patients

Example 26 NAS: entecavir

In the case of Baraclude (MA date: 26/06/2006), a Type II variation was submitted on 06/11/2013 to extend the "indication to include treatment of chronic HBV infection in paediatric patients from 2 to <18 years of age [...]", which was supported by "two juvenile toxicity studies" in rats [97].

From a clinical point of view, the new indication was supported by the following two studies of the API in the paediatric target population [97]:

- An "single-arm, open-label" Phase IIb study to evaluate the PK "safety, tolerability and efficacy" (EudraCT no.: 2005-005816-26 [91])
- A Phase III "randomized, double-blind, placebo-controlled, multicenter study" to compare the "antiviral efficacy and safety […] versus placebo" (EudraCT no.: 2009-016357-17 [91])

The extension of the indication was approved on 22/08/2014 [38].

Baraclude is not subject to the benefit assessment in Germany, because the API is not new (see Section 7.1).

Example 27 NAS: paliperidone

In the case of Invega (MA date: 25/06/2007), a Type II variation was submitted on 08/03/2013 to extend the "indication to add the treatment of schizophrenia in adolescents 15 years and older", which is supported by two toxicity studies in "juvenile rats and dogs" [98].

From a clinical point of view, the new paediatric indication was supported by the following studies for the treatment of the paediatric target population [98]:

- A Phase I "multicenter and open-label study" to "investigate the [PK] profile, safety and tolerability"
- A Phase III "randomized, multicenter, double-blind, weight-based, fixed-dose,

parallel-group, placebo-controlled study of the efficacy and safety" (Identifier: NCT00518323 [95])

- A Phase III "randomized, multicenter, double-blind, active-controlled, flexible-dose, parallel-group study of the efficacy and safety" (Identifier: NCT01009047 [95])
- A multicenter Phase III "2-year, open-label, single-arm safety study" (EudraCT no.: 2007-000577-38 [91])

The extension of the indication was approved on 23/05/2014 [38].

Invega is not subject to the benefit assessment in Germany, because the API is not new (see Section 7.1).

Example 28 NAS: oseltamivir

In the case of Tamiflu (MA date: 20/06/2002), a Type II variation was submitted on 09/07/2014 to extend the "indication to include the treatment of influenza in infants below one year of age", which was supported by "existing [PK] data" and a "[PK] study in juvenile and adult marmoset monkeys [that] has been performed to further expand the non-clinical safety package in support of the proposed indication" [100].

From a clinical point of view, "no new studies" supported the new paediatric indication, which is based on the data of two pooled PK/PD studies to evaluate its safety in the "treatment of children less than 24 months of age with confirmed influenza infection" (Identifier: NCT00391768 [95] and EudraCT no.: 2009-014365-12 [91]) that were "bridged to exposure in older children" of 1 to 12 years of age "where clinical efficacy had already been established" in the following Phase III trial [100]:

- A "double-blind, randomized, stratified, placebo-controlled study [...] in children with influenza" [99]

This approach was accepted by the CHMP, because a "formal randomised placebo controlled [...] efficacy study would have required hundreds of infants to be enrolled. Given the extensive experience with oseltamivir [...], it seemed

unnecessary to expose [a] large number of infants to either the demands of clinical trial or a placebo treatment". [100]

The extension of the indication was approved on 05/05/2015 [38].

Tamiflu is not subject to the benefit assessment in Germany because the API is not new (see Section 7.1).

Example 29 NAS: bosentan

In the case of Tracleer (MA date: 15/05/2002), a Type II variation was submitted on 07/04/2014 to extend the "indication to include treatment of symptomatic [PAH] in paediatric patients aged from 3 months to 2 years", which was supported by "three nonclinical studies [...]: an efficacy study in a model of persistent [...] (PPHN), and toxicity studies in juvenile rats" [101].

From a clinical point of view, the new indication was supported by the following open label Phase III studies in the new paediatric indication "using the paediatric formulation" [101]:

- A "multicenter study to assess the [PK], tolerability, and safety" of the API (EudraCT no.: 2004-005157-63 [91]) and the corresponding "long-term, safety, and tolerability extension study" in the paediatric patients who completed the previous Phase III study (EudraCT no.: 2005-001967-70 [91])
- A "prospective multicenter study to assess the [PK], tolerability, safety and efficacy" of the API "two versus three times a day" (EudraCT no.: 2010-021825-11 [91])

The extension of the indication was approved on 06/02/2015 [38].

Tracleer is not subject to the benefit assessment in Germany, because the API is not new (see Section 7.1).

Example 30 NAS: sildenafil

In the case of Revatio (MA date: 28/10/2005), a Type II variation was approved on 02/05/2011 to "introduce a new indication in paediatric patients aged 1 year to 17 years old" with PH [66].

"Juvenile toxicity studies were not conducted", because the existing non-clinical data "adequately addressed the potential risks for the paediatric populations" [66].

From a clinical point of view, the new indication in paediatric patients was supported by the following studies of the API in the treatment of PH [66]:

- A Phase II "randomised, double-blind, placebo-controlled, multicentre study"
- A Phase II "7-day, open-label, multicenter, [...] (PK) study (part 1)" in the treatment of PPHN (EudraCT no.: 2014-004166-23 [91])
- A Phase III multicenter study "supporting the efficacy and safety" of the new indication: "randomized, double-blind, placebo controlled, dose ranging, parallel group study" in the "treatment of children, aged 1-17 years" (EudraCT no.: 2006-002235-25) including "long-term extension" (EudraCT no.: 2005-000963-25) [91]

Revatio is not subject to the benefit assessment in Germany, because the API is not new (see Section 7.1).

Example 31 NAS: etravirine

In the case of the anti-HIV drug Intelence (MA date: 28/08/2008), a Type II variation to include the "new paediatric indication (children from the age of 6 years)" was approved on 06/03/2013.

The application was not supported by "non-clinical juvenile studies", which was "considered acceptable because the effects noted on the liver and/or thyroid were species-specific or occurred at exposures higher than that expected in humans" [102].

From a clinical point of view, the new indication was supported by a "Phase II, open-label trial to evaluate the safety, tolerability and antiviral activity" of the API in "HIV-1 infected children and adolescents" (EudraCT no.: 2007-007086-21 [91]). The CHMP concluded that an "extrapolation of efficacy data obtained in adults to children" is acceptable. The efficacy data for adults were based on two Phase III "randomized, double-blinded, placebo-controlled trial[s] to investigate the efficacy,

tolerability and safety" of the API in "HIV-1 infected subjects" (2005-003145-13 and 2005-003160-32 [91]) [102].

Intelence is not subject to the benefit assessment in Germany, because the API is not new (see Section 7.1).

Example 32 known API: everolimus

In the case of Votubia (Conditional MA date: 02/09/2011), an application for a line extension was submitted on 27/07/2012 "to add a new pharmaceutical form and three new strengths with a Type II variation to add a paediatric indication".

For this application "juvenile toxicity studies were not requested" as agreed with the "PDCO and its non-clinical expert group", because "non-clinical studies in various species did not suggest toxicity of concern for this age group" [53].

From a clinical point of view, the new indication to eliminate the "age limit 'aged 3 years and older' from the current indication" i.e. to include patients < 3 years was supported by a new Phase III "randomized, double-blind, placebo-controlled study" in the treatment of patients including 58 "subjects under 18 years" (EudraCT no.: 2007-006997-27 [91]) [53].

The extension of the indication was approved on 15/11/2013 [38].

Votubia is not subject to the benefit assessment in Germany, because everolimus is not a new API (see Table 1).

6.7.3.3.2 Non-paediatric patients

Example 33 NAS: abiraterone

In the case of Zytiga, approved on 05/09/2011 for the "treatment of [...] prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen", a Type II variation was submitted on 13/06/2012 to extend the indication to include "adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated".

The application was accompanied by several pre-clinical studies, however these are not considered as representative, because several of the submitted studies (e.g. reproduction toxicology studies, toxicology studies in juvenile animals) were not required in line with the ICH S9 guideline [(88)]. This was commented upon by the CHMP accordingly [(103)].

From a clinical point of view, the extension of the indication to include "adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy" is supported by a new multinational Phase III "randomized, double-blind, placebo-controlled study" to compare the efficacy and safety of the API in combination with prednisone versus placebo in the new patient population (EudraCT no.: 2008-008004-41 [(91)]) [(103)].

The extension of the indication was approved on 18/12/2012 [(38)].

In addition, the Phase III study that supported the application of the new indication of Zytiga was included in Module 4 A of the dossier for the benefit assessment that commenced on 15/01/2013 and reached completion on 04/07/2013. The G-BA decided that a moderate additional benefit is indicated (see Table 13). The moderate additional benefit is not considered proven, however, because the number of trial subjects (each ~500 per treatment arm) is deemed to be too small [(104), (105)].

6.7.3.4 Criterion No. 4

6.7.3.4.1 Change from combination therapy to monotherapy, or from one combination therapy to another combination

Example 34 NAS: trametinib and dabrafenib

Mekinist (NAS: trametinib) and Tafinlar (NAS: dabrafenib) were both approved on 30/06/2014 and 26/08/2013 for the treatment of "unresectable or metastatic melanoma with a BRAF V600 mutation" [106]. On 07/04/2015, a Type II variation was submitted "to add a new therapeutic indication for the use in combination of trametinib and dabrafenib" for the approved indication [106].

The application for the new indication (i.e. new combination) was supported by "two additional [in vivo] primary [PD] studies" which "examined the effect of combination dosing in a mouse BRAF mutant human melanoma xenograft model" [106]. The application referred to the non-clinical studies for the "combination treatment" of the initial "monotherapy application" for Mekinist [106].

From a clinical point of view, the new combination treatment was supported by the following two randomized Phase III studies [106]:

- A "double-blinded study comparing" the new combination to the API of Tafinlar in the approved indication (EudraCT no.: 2011-006087-49 [91])
- An "open-label study comparing" the new combination to vemurafenib in the approved indication (EudraCT no.: 2011-006088-23 [91])

The extension of the indication was approved on 25/08/2015 [38].

With the decision from 17/03/2016, the G-BA concluded that a moderate additional benefit is indicated (see Table 13) [107], [108].

Example 35 NAS: lapatinib

Tyverb was conditionally approved on 10/06/2008 "in combination with capecitabine in the treatment of […] advanced or metastatic [HER2-positive] breast cancer". On 16/02/2012, a Type II variation was submitted for the same treatment "in combination with trastuzumab".

The application was supported by a "small number of [in vitro] studies", e.g. on the "efficacy […] in combination with trastuzumab, vinorelbine, and gemcitabine" [109].

From a clinical point of view, the new combination is supported by a "randomized, multicentre, open-label Phase III study" of the API in "combination with trastuzumab versus lapatinib monotherapy" in the target patient population (EudraCT no.: 2005-003926-24 [91]) [109].

The extension of the indication was approved on 25/07/2013 [38].

Tyverb is not subject to the benefit assessment in Germany, because the API is not new (see Section 7.1).

Example 36 NAS: insulin detemir

Levemir was approved on 01/06/2004 for the "treatment of diabetes mellitus". On 07/01/2015, a Type II variation was submitted for the treatment of the same indication "in combination with GLP-1 receptor agonists".

"No new non-clinical data" were submitted [110].

From a clinical point of view, the new indication was mainly supported by a "randomised, double blind, placebo-controlled, parallel group, multi-centre, multi-national […] efficacy and safety" Phase III trial to study the "effect of [the GLP-1 receptor agonists] liraglutide versus placebo when added" to the API "with or without metformin" in "Type 2" diabetics (EudraCT no.: 2011-002696-41 [91]) [110].

The extension of the indication was approved on 27/05/2015 [38].

Levemir is not subject to the benefit assessment in Germany, because the API is not new (see Section 7.1).

Example 37 NAS: ribavirin

Rebetol was approved on 07/05/1999 for the "treatment of chronic hepatitis C […] as part of a combination regimen with peginterferon alfa-2b or interferon alfa-2b" [(111)]. On 30/11/2011, a Type II variation was submitted "to reflect the triple combination use" of the API of Rebetol together with peginterferon alfa 2b and boceprevir in the "treatment of Hepatitis C" [(111)].

Non-clinical aspects are not mentioned in the corresponding VAR.

From a clinical point of view, the new indication is mainly supported by two Phase III safety and efficacy studies of boceprevir in "subjects with chronic hepatitis C" [(111)]:

- Study in "previously untreated subjects" (EudraCT no.: 2007-005508-42 [(91)])
- Study in subjects "who failed prior treatment with peginterferon / ribavirin" (EudraCT no.: 2007-005151-42 [(91)])

The extension of the indication was approved on 30/03/2012 [(38)].

Rebetol is not subject to the benefit assessment in Germany, because the API is not new (see Section 7.1).

Example 38 NAS: linagliptin

Trajenta was approved on 24/08/2011 for the treatment of "Type 2 diabetes mellitus to improve glycaemic control […] as monotherapy" and "in combination" with a) metformin and b) "a sulphonylurea and metformin". On 14/03/2012, a Type II variation was submitted to extend the indication for the "treatment of Type 2 diabetes in combination with insulin (with or without metformin)".

No new non-clinical data were submitted [(112)].

The new indication as "add-on to insulin" is mainly supported by a new Phase III "randomized, double-blind, placebo-controlled, parallel group efficacy and safety study" of the API "in combination with basal insulin" (EudraCT no.: 2008-008296-33 [(91)]) [(112)].

The extension of the indication was approved on 24/10/2012 [38].

Trajenta is subject to benefit assessment due to its new API, but no benefit dossier was submitted to the G-BA for the new indication. The reason could be that the initial benefit assessment already caused the G-BA to decide that the additional benefit is considered as not proven because of the incomplete nature of the dossier. Given the lack of the benefit dossier, the additional benefit for the new indication is considered as not proven (see Table 13).

6.7.3.4.2 Change from the first line treatment to second line treatment or vice versa

Example 39 API: eribulin

In the case of Halaven, approved on 17/03/2011 for the "treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least *two* chemotherapeutic regimens for advanced disease", a Type II variation was submitted on 04/04/2013 to extend the indication to include "patients [...] who have progressed after at least *one* chemotherapeutic regimen for advanced disease", i.e. to "extend the indication from the current 3rd line treatment to 2nd line treatment".

The application was accompanied by a selection of "in vitro and in vivo" primary PD study data. The CHMP concluded that these data "do not allow extrapolation to the clinical situation", but that they "indicate a plausible biological mechanism for some part of the difference between overall survival and progression-free survival" that was observed in the Phase III study [113].

From a clinical point of view, the new indication is mainly supported by the new "Phase III open label, randomized two-parallel-arm multicenter study", comparing the "efficacy and safety of eribulin and capecitabine monotherapy in the first - third line setting". In addition, "clinical pharmacology" aspects of this application are supported by an "updated population [PK]" analysis and a new "PK/PD analysis" (EudraCT no.: 2005-004009-26 [91]). On clinical safety, the CHMP concluded that, as one of the "important identified risks", the "long-term resolution

of peripheral neuropathy" would be "addressed in a planned" Phase III study that is part of the RMP [113].

The extension of the indication was approved on 27/06/2014 [38].

The Phase III study that supported the application for the new indication of Halaven is included in Module 4 A of the dossier for the benefit assessment that commenced on 01/08/2014 and reached completion on 22/01/2015. The G-BA decided that the additional benefit is proven to be moderate for the Phase III study population, i.e. "patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes" (see Table 13) [114], [115].

6.7.3.5 Change from treatment to prevention[43] or diagnosis of a disease (Criterion Nos. 5 & 6)

Example 40 known API: denosumab

Xgeva was approved on 13/07/2011 for the "prevention of skeletal related events [...] in adults with bone metastases from solid tumours". A Type II variation application was submitted on 06/12/2012 to include the "treatment of [GCT] of bone", which did not include "new non-clinical data" [116].

From a clinical point of view, the new indication of Xgeva – which is not subject to the "benefit assessment"[44] in Germany – is supported by two new "open-label, multi-centre" Phase II safety and efficacy studies (EudraCT no.: 2006-006964-48 and 2008-001606-16 [91]). The CHMP concluded that the "long-term effects need to be further addressed" and that "further safety follow-up is needed" as proposed with the "long-term safety follow-up" of subjects of the latter Phase II study "which is part of the agreed RMP" [116].

The extension of the indication was approved on 01/09/2014. [38].

[43] Including prevention of progression/relapses of a disease

[44] Although the benefit assessment began on 15/10/2013, it was terminated on 17/04/2014 due to the omission of § 35a(6) SGB V and because the API was not new (see Section 7.1).

The benefit assessment was terminated due to the omission of § 35a(6) SGB V (see Table 1).

6.7.3.6 Change from short-term treatment to long-term maintenance therapy in chronic disease (Criterion No. 7)

Example 41 NAS: dasatinib

In the case of Sprycel (MA date: 20/11/2006), a Type II variation to include the "treatment of adults with newly diagnosed [...] (CML) in chronic phase" was approved on 06/12/2010.

The application included a "very brief summary of the status of the recently-completed (in-life portion) carcinogenicity study in rats, as it is recognised these data are considered of relevance in view of the expected long treatment duration of newly diagnosed CML patients" [64].

From a clinical point of view, the new indication is supported by a new "open-label, randomized, multicenter Phase III trial of [...] [the API] vs. standard dose imatinib (400 mg) in the treatment of subjects with newly diagnosed *chronic phase* Philadelphia chromosome positive" CML (EudraCT no.: 2006-005712-27 [91]) [64].

Sprycel is not subject to the benefit assessment in Germany, because the API is not new (see Section 7.1).

Example 42 NAS: dabigatran etexilate mesilate

For the initial MAA of Pradaxa (MA date: 18/03/2008), "no carcinogenicity studies have been submitted since [...] [the API] will not be regularly administered over a substantial part of patient's lifetime" [117]. On 05/01/2010, an application for a line extension was submitted to include the "prevention of stroke and systemic embolism in adult patients with [NVAF]" [81].

According to Section 4.2 of the SmPC, this new indication is subject to long-term

treatment [118]. Consequently, the application for the extension of the indication is supported by carcinogenicity studies [81].

From a clinical point of view, the new indication is "mainly supported by one pivotal trial enrolling 18113 patients", which is a "prospective, multi-centre, parallel-group, non-inferiority" Phase III trial for the "randomized evaluation of *long term* anticoagulant therapy [...] comparing the efficacy and safety of two blinded doses of [the API] dabigatran etexilate with open label warfarin" for the new indication (EudraCT no.: 2005-003894-26 [91]) [81].

The extension of the indication was approved on 01/08/2011 [38].

Pradaxa is not subject to the benefit assessment in Germany. Although the benefit assessment began on 01/12/2013, it was terminated on 17/04/2014 due to the omission of § 35a(6) SGB V and because the API was not new (see Section 7.1) [148].

Example 43 NAS: fondaparinux

In the case of Arixtra (MA date: 14/02/2001), a Type II variation "to include treatment of adult patients with acute symptomatic spontaneous [SVT] of the lower limbs without concomitant [DVT]" was approved on 31/08/2010.

In the initial MAA "a large number of [toxicology] studies were performed in […] rats and in Cynomolgus monkeys with maximal treatment duration of 3 months" [119]. "Following a Scientific Advice from the CHMP" an "additional 6 month repeat dose toxicity study [...] in the rat" was requested [121]. The reason could be that the new indication is approved for an increased[45] treatment period "up to a maximum of 45 days" according to Section 4.2 of the SmPC [120].

From a clinical point of view, the new indication is supported by an "international, multicentre, randomised, double-blind, placebo-controlled, two-parallel group, Phase III study to evaluate the efficacy and safety of Arixtra" for the treatment of

[45] For the initial indication the "intended treatment duration […] is less than one month". [119]

the new indication (EudraCT no. 2006-004774-27 [91]) [121].

Arixtra is not subject to the benefit assessment in Germany, because the API is not new (see Section 7.1).

7 Market access for reimbursable MPs with extended indications in Germany

Reimbursable MPs include prescription MPs only, with the exception of the following[46]:

- Prescription MPs against trivial diseases, i.e. MPs to treat the common cold or travel-sickness, laxatives and therapeutic MPs for mouth and throat[47]
- Prescription MPs that focus on increasing quality of life (e.g. MP that serve to increase virility or promote smoking cessation, weight loss, hair growth)

7.1 Benefit assessment in accordance with § 35 a SGB V[48] [122]

7.1.1 General background

Since 01/01/2011, pharmaceutical companies are obliged to submit a benefit dossier as soon as a reimbursable MP with a new API "is launched on the German market" [122]. "This also applies to newly authorized indications of these pharmaceuticals"[49], meaning that the benefit assessment pertains to extensions of indications that result from Type II variations[50] [122]. For extended indications that have been approved within new MAs on the legal basis of Article 8(3) (see Tables 1 and 2) or Article 10(3) (see Table 3), the obligation to submit a benefit dossier depends on whether or not the API was launched on the German market after 01/01/2011 for the first time.

[46] § 34(1) SGB V

[47] With the exception of those used in the treatment of fungal infections

[48] §§ 3-7 AM-NutzenV and Chapter 5 VerfO

[49] § 3 AM-NutzenV

[50] § 2(2) VerfO

The relevant time for the first launch on the German market is the publication of the MP in a specific register, namely the "Lauer-Taxe" [51] [(123)].

Based on the submitted dossier (see Section 7.2), the G-BA "assesses recognition of any additional benefit claimed over the appropriate comparator" [(122)].

The following categories for the quantification of additional benefit are defined[52]:

- Major ("erheblich")
- Moderate ("beträchtlich")
- Minor ("gering")
- Not quantifiable
- Not proven
- Lower than benefit of comparator

The assessment is performed by the G-BA or on its behalf by the IQWiG "within three months of market authorisation" [(122)]. After publication "pharmaceutical companies, federations, and experts are given the opportunity to submit written and verbal statements" on the "result of the benefit assessment" [(122)]. Three months later, the G-BA "passes a resolution" [(122)]. Where the indication is extended for an MP that has already been assessed by the G-BA the benefit assessment is amended accordingly, i.e. the resolution of the G-BA summarises the extent of additional benefit across all indications [(124)].

The following distinctions apply:

- The additional benefit will be considered as not proven, if the dossier is not submitted completely by the time the MP is launched on the market for the first time
- For OMPs, the additional benefit will be considered as proven automatically if the annual turnover is less than € 50 million. Nevertheless, OMPs "have to submit a limited dossier that states the value" of the additional benefit [(125)] [53].

[51] §8 Nr. 1 VerfO

[52] § 5(7) VerfO

[53] §35a(1) SGB V in conjunction with §12 VerfO

An example is the OMP Ofev (see Table 2), for which the additional benefit is considered as inherent [126]

- The pharmaceutical company can be exempted from the obligation to submit a benefit dossier upon request, if it is expected that the annual expenditure incurred by the SHI is less than € one million for the MP[54]. Should the new indication for an MP that has been exempted from the obligation to submit a benefit dossier lead to a turnover that exceeds € one million, upon request by the G-BA a benefit dossier must be submitted by the pharmaceutical company within 3 months [55]
- MPs are exempted from the obligation to submit a benefit dossier if the new indication does not lead to a turnover that exceeds € one million. This applies to MPs "for hospital use only" [127]: "If a product is set to be used exclusively in a hospital setting, the company may file for exemption from submitting a dossier […] The idea behind this is that the SHI will not face additional costs as payment in the hospital sector is organized via a DRG-based system" [125]. This is reflected by the corresponding form for the exemption application: the calculation of the expected costs for the SHI considers the number of patients that are subject to *outpatient care* only [128] (see Examples 44 and 45)
- As § 35a(6) SGB V has been omitted, no benefit dossier needs to be submitted for extensions of indications of MPs with an initial benefit assessment that was conducted on the legal basis of § 35a(6) SGB V, as shown in Example 46

Example 44 known API: dexmedetomidine

In the case of Dexdor (authorisation date: 16/09/2011; legal basis: Article 8(3)), which is "for hospital use only", the G-BA accepted the application for exemption from the benefit assessment [129], [130].

Example 45 known API: defibrotide

In the case of the OMP Defitelio (authorisation date: 18/10/2013; legal basis: Article 8(3)), which is "for hospital use only", the G-BA accepted the application for exemption from the benefit assessment [131], [132].

[54] §35a(1a) SGB V in conjunction with §15 VerfO (Chapter 5, Section 3)

[55] §15(4) VerfO

Example 46 NAS: saxagliptin

In the case of Onglyza[56] (MA date: 01/10/2009; date of the initial benefit assessment: 01/10/2013), a new indication was approved on 26/07/2013. The corresponding benefit assessment procedure began on 01/09/2013. Given the omission of the legal basis of § 35a(6) SGB V, the ongoing procedure was terminated on 17/04/2014 (133) (see Table 14).

7.1.2 Relevance for extensions of indications

One result of the EPAR research (see Section 4.1) identified 237 CAPs with extensions of indications that result from Type II variations. A closer look at these cases reveals the following:

- For 22 CAPs authorised after 01/01/2011, a benefit assessment was conducted (see Table 13)
- For 12 CAPs (see Table 14) a benefit assessment was conducted, although these MPs were authorised before 01/01/2011. The legal basis for this benefit assessment was § 35a(6) SGB V, which was applicable at the time, but omitted by the 14. SGB V-ÄndG with affect from 01/01/2014
- For 7 CAPs authorised after 01/01/2011, no benefit assessment has been conducted. Possible reasons are:
  - The MP is not marketed in Germany or
  - The MP has been exempted from the benefit assessment or
  - Another MP containing the same API was initially marketed in Germany before 01/01/2011 (example: Prolia/Xgeva[57]; see Table 1)

A further result of the EPAR research identified the following CAPs approved after 01/01/2011 with extended indications on the legal basis of Article 8(3):

[56] Other examples of a benefit assessment for a new indication of an MP with an initial benefit assessment conducted on the legal basis of § 35a(6) SGB V could not be identified.

[57] The benefit assessment of Xgeva (API: denosumab) was terminated due to the omission of § 35a(6) SGB V.

- The CAPs that contain a *NAS* are shown in Table 2. In four cases the benefit has been assessed in accordance with § 35a SGB V
- The CAPs that contain a *known API* are shown in Table 1. In one case the benefit has been assessed pursuant to § 35a SGB V

The definition for an MP with a new API is applicable as long as the data protection period has not expired[58]. In general, this means that the benefit assessment should not be applicable for extensions of indications that have been approved with a new MA on the legal basis of Article 10(3), because in these cases the data protection period has expired. One counterexample is the OMP Raxone (see Table 3). A potential reason could be that the API of Raxone, idebenone, was first launched on the German market on 01/10/2015, i.e. later than 01/01/2011 (134).

7.2 Benefit dossier

It is necessary to update the benefit dossier in the case of reimbursable MPs with indications that have been extended via a Type II variation, and which are affected by the benefit assessment.

In Module 2, which includes basic information on the MP and its indications, the new indication needs to be listed, and a separate code ("A-Z") needs to be assigned. This code must be referred to throughout the dossier (135).

In addition, the indication specific Modules 3 and 4 need to be written for the new indication.

The following needs to be defined in Module 3 (136):

- Appropriate comparator
- Number of patients[59] with therapeutically meaningful additional benefit
- Annual costs for the SHI
- Description of the requirements on the quality assured medication

[58] § 2(1) VerfO

[59] Insured by SHI

In Module 4, the following must be presented [137]:

- Method and results of the valuation of the (additional) benefit
- Patient group(s) with therapeutically meaningful additional benefit
- Final conclusion on the valuation of the (additional) benefit

Finally, the dossier summary in Module 1 needs to be updated accordingly, e.g. as concerns the annual costs for the SHI for all patients and for patient groups with therapeutically meaningful additional benefit. Both of these points must be summarised across all indications [138] to which the dossier refers.

7.3 Reimbursement price

7.3.1 General background

For MPs with additional benefit the SHI and the pharmaceutical company "negotiate the reimbursement price paid by the [SHI] funds" [122]. Where the reimbursement price has already been negotiated for an MP this price needs to be renegotiated in the case of a new indication, and the new reimbursement price directly replaces the initial one [124].

This is done within 6 months, and the reimbursement price is valid from the 13th month of market launch [122] [60].

The sales prices in 15 EU countries (BE, DK, FI, FR, GR, GB, IE, IT, NL, AT, PT, SE, SK, ES and CZ) are used as the basis for the price negotiation. These are weighed according to turnover and PPPs [139].

The following distinctions apply:

- "If no agreement is reached", the reimbursement price is determined in an arbitration procedure that uses "European pricing levels as its standard" [122] [61]

[60] § 130b SGB V

[61] § 130b(4) SGB V

- "If the G-BA decides" that "any additional benefit over the appropriate comparator" is lacking for the new MP, and if a reference price cannot be set (see Section 7.4), then "a reimbursement price will also be agreed on", but the reimbursement price will not exceed "the annual treatment costs" of the "appropriate comparator" (122) [62]

Where the new indication leads to an additional benefit, which is significantly different from the initial additional benefit, the transition period between the approval of the new indication and the negotiation of the new reimbursement price can be considered, e.g. by means of retrospective reimbursement (124).

The SHI handles this reimbursement price confidentially, i.e. it is published on the website of the SHI only if the pharmaceutical company is in agreement. Commonly pharmaceutical companies do not consent to the publication of the reimbursement price because this may have adverse effects on the global market price. This is because the price in Germany serves as a reference price for several other countries (140): in the EU, 17 countries make reference to the German price. Examples of non-EU countries that refer to the German price are Canada, Japan, South Korea and Switzerland (141).

Finally, the reimbursement price "takes the form of a rebate on the retail price originally set by the company". The pharmaceutical company grants this rebate, and the wholesaler and the pharmacies pass it to the SHI (122) [63].

7.3.2 Relevance for extensions of indications

For 22 MPs with extensions of indications that result from Type II variations and were approved after 01/01/2011, a benefit assessment has been conducted (see Table 13). For 17 MPs, a reimbursement price exists. For three MPs (Opdivo, Mekinist, Xultophy) the reimbursement price is not yet available. The other two MPs (Trajenta, Xiapex) opted out.

[62] § 130b(3) SGB V

[63] § 130b(1) SGB V

In several cases, the G-BA decided that the additional benefit is not proven (e.g. Eviplera, Eylea, Gilenya, Komboglyze, Stivarga, Tresiba, and Yervoy) for the extended indication. The reimbursement price is not published. Nevertheless, it is thought that in these cases the extension of the indication does not lead to an increase of the reimbursement price.

In some cases the G-BA decided that a minor or moderate additional benefit applies to (a part of) the new indication(s) (e.g. Eliquis, Halaven, Jakavi, Kalydeco, Tafinlar, Xtandi and Zytiga). The reimbursement price is not published. Nevertheless, when additional benefit is proven and the annual costs for the comparator are increased for the new indication, this can potentially result in an increased reimbursement price. Examples are Elquis, Halaven, Kalydeco, Tafinlar and the OMP Xtandi.

The results of the benefit assessment of MPs approved after 01/01/2011 with extended indications on the legal basis of Article 8(3) and that contain an *NAS* are shown in Table 2. Example 47 shows a possible effect of the extension of an indication on the reimbursement price.

Example 47 NAS: aflibercept

Eylea was initially approved on the legal basis of Article 8(3) on 22/11/2012 for the treatment of neovascular (wet) AMD. The G-BA decided that the additional benefit is not proven, and the assessment was closed on 15/12/2015. A reimbursement price was agreed but not published. As the additional benefit is considered “not proven”, the reimbursement price is expected to be lower than the price of the comparator, i.e. lower than € 11,284 (annual costs/patient). However on 01/02/2013, Zaltrap was approved on the legal basis of Article 8(3) for the treatment of MCRC. The G-BA decided that the additional benefit is minor, and the assessment was closed on 15/08/2013. A reimbursement price was agreed but not published. Due to the result of the benefit assessment the reimbursement price is expected to be between the price of the comparator and the initial price, i.e. between € 20,514 and € 57,331 (annual costs/patient) (see Table 2).

7.4 Reference price

"If the G-BA decides" that there is no "additional benefit over the appropriate comparator" to the new MP, a reference price will be assigned "within six months of market launch", if this is possible (122) [64].

The reference price is the "maximum amount, which is reimbursed by the [SHI] fund". If the price of an MP exceeds the reference price, the "patient generally pays the difference to the reference price or receives a therapeutically comparable medicinal product" (142).

In general, inclusion into the reference price system is possible as long as the MP contains an *off-patent* API and providing the MP can be included together with other reference price candidates in one of the following groups (142):

- group of the "same active ingredients" or
- group of "pharmacologically-therapeutically comparable active ingredients" or
- group of a "therapeutically comparable action" [65]

There is one exception where a reference price can be applied for *patent* MPs. This exception applies when at a minimum three MPs can be included into a reference price group of "pharmacologically-therapeutically comparable" (142) APIs that do not represent a therapeutic enhancement as a result of improved efficacy or reduced side effects.[66]

Based on the identified MPs with indications extended via a Type II variation (see Tables 2, 13 and 14), it becomes apparent that the reference price system has not been applied. This is considered logical because in general a new indication for the same API is expected to represent a therapeutic enhancement.

[64] § 130b(3) SGB V

[65] § 35(1) SGB V

[66] § 35(1a) SGB V

7.5 Cost-Benefit-Assessment

Since the AMNOG entered into force on 01/01/2011, the cost-benefit-assessment is only foreseen in the following cases:

- Upon request of the pharmaceutical company or SHI if the arbitration is not accepted [67]
- Upon request of the pharmaceutical company if the resolution of the G-BA does not claim any additional benefit [68]

So far, only one cost-benefit-assessment is available. It was conducted for Venlafaxin, Duloxetin, Bupropion and Mirtazapin (143). Therefore, the present study does not consider the cost-benefit-assessment for MPs with extended indications in further detail.

According to the IQWiG, the future relevance of the cost-benefit-assessment in the German health care system remains to be seen (144).

8 Summary

The extension of an indication to include a “new indication” can be based on different criteria, i.e. on 1. “a new target disease”, 2. “different stages or severity of a disease”, 3. “an extended target population”, 4. “change from” 1st line to 2nd line treatment (or vice versa), or change of the combination therapy, 5. & 6. “change from treatment to prevention or diagnosis”, or 7. “change from short-term [...] to long-term“ treatment (see Chapter 2).

An extension of an indication can be achieved in different ways:

- When the strength, pharmaceutical form and route of administration and the INN of the MP remain unchanged the common approach is to apply for a Type II variation of Category C.I.6.a. When the strength, pharmaceutical form or route of administration changes in parallel and the INN of the MP remains

[67] § 135b(8) SGB V

[68] § 35a(5a) SGB V

unchanged an extension of indication can be included in a line extension by grouping (see Section 3.1)

- When the INN of the MP changes with the new indication or when a non-orphan MP is authorised for an orphan indication, a new MA needs to be applied for. This is either according to Article 10(3) for a hybrid application or according to Article 8(3). The application according to Article 8(3) is chosen when a full set of data is presented and no reference is made to non-clinical or clinical data of a reference MP (see Section 3.2.1). The hybrid application is chosen when non-clinical or clinical data of both the MP and the reference MP are included (see Section 3.2.2).

By extending the indication as early as possible after the initial MA, the MAH profits as long as possible from market exclusivity. This becomes apparent with the following results of the EPAR research (see Section 4.1):

- To date, most of the Type II variations to extend the indication have been submitted 2-3 years after the submission of the initial MAA, and
- extensions of indications have been submitted later than 15 years after the initial MA only in rare cases

Furthermore, the EPAR research shows that 30% of the analysed MPs were subject to one to four Type II variations to extend the indication, and that 2-3% were subject to five or more Type II variations to extend the indication. In the case of ten CAPs, extensions of indications were included in line extensions (see Section 4.2).

Of the 349 MAs approved on the legal basis of Article 8(3), fifteen MPs introduced extended indications with the new MA. In 56 cases only a case-by-case evaluation could determine whether or not new indications had been introduced with the new MA, which was not pursued in the present study. As concerns the timing of extensions of indication submitted on the legal basis of Article 8(3), considerations about data or market protection periods are not relevant (see Section 4.3).

For extensions of indications introduced with a new MA in accordance with Article 10(3), a total of seven of hybrid applications could be identified. This rareness may

be explained by the fact that these MPs can only be marketed after the expiration of the market protection period of the reference MP (see Section 4.4).

The following different incentives for extensions of indications *may* be applicable, which mainly aim at the extension of the data or market exclusivity:

- One year of data exclusivity for the study data of a new indication for a well established substance[69] - no publication of the acceptance of such an extended data exclusivity can be found for CAPs (see Section 5.1)
- Additional one year of market protection in the case of an extended indication with "significant clinical benefit"[70] and which is authorised within eight years upon the submission of the initial MA. Publications of the acceptance of such an extended data exclusivity are found for 18 CAPs (see Section 5.2)
- PUMA for off-patent MPs - currently two PUMAs have been approved (see Section 5.3)
- Extended market exclusivity for OMPs when the new orphan indication receives a separate ODD – three cases are identified (see Section 5.4)
- Patent for the new indication for off-patent APIs or additional 6 months SPC – the latter is not directly linked to the extension of an indication (to include a paediatric indication), because it is granted irrespective of the results of the paediatric studies (see Section 5.5)

The regulatory assessment and the dossier requirements for Type II variation to extend the indication include the following aspects:

- Update of the SmPC and PL & user consultation (see Section 6.1)
- Update of ERA, where applicable (see Section 6.2)
- For orphan MPs, only: designation of a separate ODD or inclusion of new indication into existing ODD and non-similarity assessment, as applicable (see Section 6.3)
- PSUR cycle adaption (see Section 6.4.1), additional monitoring and adaption of review frequency for signal management (see Section 6.4.2), where applicable
- RMP update (see Section 6.4.3)

[69] Article 10(5) of Directive 2001/83/EC

[70] Article 14(11) of Regulation (EC) No 726/2004

- Submission of PIP compliant studies, or a product-specific waiver, or a class waiver or a deferral decision - each covering both the approved and the proposed indication (see Section 6.5)
- Update of quality modules:
    - In the case of the grouping with changes to strength, pharmaceutical form or route of administration within a line extension (see Section 6.6.1)
    - In the case of other consequential changes that are grouped with the extension of an indication, e.g. up-scaling (see Section 6.6.2)
- Update of the pre-clinical modules (see Section 6.7.1):
    - Primary PD studies may be necessary in the case of a new target disease (Criterion No. 1)
    - In the case of an extended target population (Criterion No. 3) to include paediatric patients, toxicity studies in juvenile animals should only be conducted where there is a specific concern
    - In the case of a change of the combination therapy (Criterion No. 4), toxicity studies on the combination are only recommended when appropriate clinical experience with the combination is lacking
    - In the case of a change from short-term to long-term treatment (Criterion No. 7), carcinogenicity studies are generally required, except for oncologic MPs. In specific cases, additional repeated-dose toxicity studies might be needed to cover the recommended durations
- Update of the clinical modules (see Section 6.7.2) to include the clinical studies that support the new indication both from a regulatory and market access point of view, i.e. Phase III RCTs

For the access of reimbursable MPs with extended indications to the German market, a benefit assessment in accordance with § 35 a SGB V needs to be considered. This applies to MPs with extensions of indications that result from Type II variations or that have been approved with a new MA on the legal basis of Article 8(3) or Article 10(3), whenever the respective API was launched on the German market for the first time after 01/01/2011. For these MPs, a benefit dossier needs to be submitted to the G-BA, which must “prove an additional benefit [...] over the appropriate comparator” [122] to gain the highest possible reimbursement price (see Section 7.1.1).

This benefit dossier needs to be updated: in Module 2 the new indication must be listed, the indication specific Modules 3 and 4 need to be written for the new indication just as the dossier summary in Module 1 requires updating (see Section 7.2).

For MPs with additional benefit, a reimbursement price is negotiated or renegotiated, as applicable (see Section 7.3.1).

An overview of benefit assessments and reimbursement prices is given for the MPs with extended indication that have been approved after 01/01/2011 (see Sections 7.1.2 and 7.3.2).

Generally, neither reference prices (see Section 7.4) nor cost-benefit-assessments (see Section 7.5) are relevant for the market access of MPs with extensions of indications in Germany.

In sum, the present thesis provides orientation on the regulatory background of extensions of indications in the EU, including aspects on market access in Germany. In order to establish practical relevance of the different topics for RA employees, various examples are provided across the different chapters.

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Table 1 Known APIs with indications extended via Article 8(3), authorised later than 01/01/2011

Name of the CAP [38]	**MA date** [38]	**Authorised Indications** [38]	**API** [38]	**Indication specific EURD** [147]	**Indication** [147]	**Benefit assessment according to § 35a(1) SGB V** [148]
Ameluz	14/12/2011	See b)	5-aminolevulinic acid	a) and b) 07/09/2007	a) Glioma b) Keratosis	-
Bronchitol[72]	13/04/2012	See b)	mannitol	a) not provided b) 13/04/2012	a) All indications apart from CF b) CF	-
Enurev Breezhaler, Seebri Breezhaler, Tovanor Breezhaler	28/09/2012	See b)	glycopyrronium bromide	a) not provided b) 28/09/2012	a) all indications except for COPD b) COPD	-
Esmya	23/02/2012	See b)	ulipristal	a) 15/05/2009[73] b) 23/02/2012	a) female emergency contraceptive b) treatment of moderate to severe symptoms of uterine fibroids	-
Jinarc	27/05/2015	See b)	tolvaptan	a) 03/08/2009[74] b) 27/05/2015	a) Treatment of adults with hyponatraemia secondary to SIADH b) Treatment of adults with	-

[72] OMP

[73] Please refer to the MP “ellaOne“.

[74] Please refer to the MP “Samsca“.

Name of the CAP [38]	**MA date** [38]	**Authorised Indications** [38]	**API** [38]	**Indication specific EURD** [147]	**Indication** [147]	**Benefit assessment according to § 35a(1) SGB V** [148]
					ADPKD	
Votubia[75]	02/09/2011	c) (Renal angiomyolipoma associated with TSC & SEGA associated with TSC)	everolimus	a) 08/07/2003 b) 03/08/2009 c) 02/09/2011	a) Rejection of transplanted organs b) RCC c) Astrocytoma	-
Xgeva	13/07/2011	See b)	denosumab	a) 26/05/2010[76] b) 13/07/2011	a) osteoporosis and for bone loss associated with hormone ablation in prostate cancer b) skeletal related events associated with bone metastases and for GCT of bone	- [77]
Xiapex	28/02/2011	See b)	collagenase Clostridium histolyticum	a) 12/12/1969 b) 28/02/2011	a) all indications except for treatment of Dupuytren's contracture and Peyronie's disease	X [149]

[75] Conditionally approved orphan MP

[76] Please refer to the MP „Prolia".

[77] Procedure terminated due to the omission of article § 35a(6) SGB V

Name of the CAP [38]	**MA date** [38]	**Authorised Indications** [38]	**API** [38]	**Indication specific EURD** [147]	**Indication** [147]	**Benefit assessment according to § 35a(1) SGB V** [148]
					b) treatment of Dupuytren's contracture and treatment of Peyronie's disease	

Table 2 NAS with indications extended via Article 8(3), authorised later than 01/01/2011
Table 2.1

Name of the CAP	MA date (submission date of MAA) [38]	Authorised indications [38]	API [38]	Indication specific EURD [147]	Indication [147]
Eylea	22/11/2012 (31/05/2011)	See b)	aflibercept	a) 03/08/2012 b) 22/11/2012	a) oncological indication(s) b) wet macular degeneration and CRVO
Zaltrap	01/02/2013 (24/11/2011)	See a)			
Vargatef	21/11/2014 (30/09/2013)	See b)	nintedanib	a) 15/10/2014 b) 21/11/2014	a) respiratory indication b) oncology indications
Ofev[78]	15/01/2015 (05/05/2014)	See a)			
Kolbam[79]	04/04/2014 & 20/11/2015[80] (29/02/2012)	See b)	cholic acid	a) 12/09/2013 b) 04/04/2014	a) oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication b) CTX, AMACR, or cholesterol 7α-hydroxylase deficiency indication

[78] Orphan

[79] Orphan

[80] Revised CHMP opinion [150]

Table 2.2

Name of the CAP	**Benefit assessment according to § 35a(1) SGB V** [148]	**Annual costs for the comparator € / patient according to module 1** [148]	**G-BA decision on additional benefit** [148]	**Annual costs for the comparator € / patient** [151]	**In the case of additional benefit: initial price €** [151]	**Reimbursement price** [151]
Eylea[81]	15/12/2012	11,965[82] - 18,484[83]	not proven	0 – 11,284	n. a.	Agreed but not published
Zaltrap	15/08/2013	11,309	minor	20,514	57,331	
Vargatef	18/06/2015	25,234 – 74,046	minor	No information available (yet) [151]		
Ofev[84]	03/09/2015	-	minor			
Kolbam[85]	-					

[81] Please also refer to Table 13

[82] According to SmPC

[83] According to DDD

[84] Orphan

[85] Orphan

Table 3 MPs with indications extended via hybrid application

Name of the CAP	MAH [38]	MA date [38]	API [38]	EURD [147]	Reference MP [38]	MAH of reference MP [38]	Benefit assessment according to § 35a(1) SGB V [148]
Buccolam	ViroPharma SPRL	05/09/2011	midazolam	oromucosal solution, treatment of prolonged, acute, convulsive seizures: 05/09/2011 other: 10/09/1982	Hypnovel	Roche Products Ltd.	-
Nexium Control	Pfizer Consumer Healthcare Ltd	26/08/2013	esomeprazole	10/03/2000	Nexium	AstraZeneca AB	-
Controloc Control / Pantecta Control / Pantoloc Control / Pantozol Control / Somac Control	Takeda GmbH	12/06/2009	pantoprazole	23/08/1994	Pantozol	Nycomed GmbH	-
Raxone[86]	Santhera Pharmaceuticals GmbH	08/09/2015	idebenone	30/09/1986	Mnesis	Takeda Italia Farmaceutici S.p.A	x (Procedure ongoing)

[86] Orphan

Name of the CAP	**MAH** [38]	**MA date** [38]	**API** [38]	**EURD** [147]	**Reference MP** [38]	**MAH of reference MP** [38]	**Benefit assessment according to § 35a(1) SGB V** [148] [154]
Topotecan Hospira	Hospira UK Ltd	10/06/2010	topotecan	12/11/1996	Hycamtin	SmithKline Beecham Plc	-
Zalviso	Grünenthal GmbH	18/09/2015	sufentanil	30/11/1978	Sufenta	Janssen-Cilag B.V.	-
Zyclara	Meda AB	23/08/2012	imiquimod	18/09/1998	Aldara	see Zyclara	-

Table 4 Number of procedures for MAAs for Biosimilars 2003 – 2016 [38]

Procedure started in / Outcome[87]	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016[88]
Not yet available[89]	-												12	1[90]
Authorised	-	1[91]	-	4[92]	6[93]	-	1[94]	-		5[95]	1[96]	2[97]	-	
Withdrawn after authorisation	-	1[98]	-		1[99]	-								
Refused	1[100]	-										1[101]	-	

[87] Excluded MAAs „withdrawn prior to opinion“, if an outcome is available [145]
[88] Up to February 2016
[89] Procedure started [145]
[90] Forecast for 2016: 8 [146]
[91] Omnitrope
[92] Abseamed, Binocrit, Epoetin Alfa Hexal, Silapo
[93] Biograstim, Filgrastim Hexal, Ratiograstim, Retacrit, Tevagrastim, Zarzio
[94] Nivestim
[95] Bemfola, Grastofil, Inflectra, Ovaleap, Remsima
[96] Abasaglar
[97] Accofil, Benepali
[98] Valtropin
[99] Filgrastim ratiopharm
[100] Alpheon
[101] Solumarv

Table 5 MPs with extended indications submitted via type II variation application more than 15 years after the submission of the initial MAA

Name of the CAP	API	MA date	Submission date	
			Initial MAA	Latest type II variation to extend the indication
BeneFIX	nonacog alfa	27/08/1997	16/08/1996	08/03/2012
Enbrel	etanercept	03/02/2000	13/10/1998	05/11/2013
MabThera	rituximab	02/06/1998	27/02/1997	13/04/2012
Rebetol	ribavirin	07/05/1999	29/05/1998	07/07/2014
Sustiva	efavirenz	28/05/1999	29/06/1998	17/01/2014
Taxotere	docetaxel	27/11/1995	07/09/1994	not before 19/02/2010[102]

[102] This date is estimated by subtracting 90 days from the CHMP opinion, dated 20/05/2010. About the same time, i.e. on 26/01/2010, the generic Docetaxel Teva was approved. (38)

Table 6 Subset of type II variations to extend the indication that are embedded in line extensions

Name of the CAP [38]	API [38]	MA date [38]	Approval date(s) for line extension(s) including type II variation(s) to extend the indication
Eliquis	apixaban	18/05/2011	19/11/2012
Intelence	etravirine	28/08/2008	06/03/2013
Isentress	raltegravir	20/12/2007	22/08/2014
Pegasys	peginterferon alfa-2a	20/06/2002	13/03/2013
Pradaxa	dabigatran etexilate mesilate	18/03/2008	01/08/2011
Prezista	darunavir	12/02/2007	24/10/2012
Revlimid[103]	lenalidomide	14/06/2007	10/09/2012 and 19/02/2015
Revolade	eltrombopag	11/03/2010	19/09/2013
Viread	tenofovir disoproxil fumarate	05/02/2002	22/11/2012
Votubia[104]	everolimus	02/09/2011	15/11/2013

[103] OMP

[104] Conditionally approved OMP

Table 7 MPs with additional one year of market protection for the new indication with "significant clinical benefit" according to Article 14(11) of Regulation (EC) No 726/2004

Name of the CAP	MA date [38]	API [38]	Approval date of new indication" with "significant clinical benefit" [38]	Procedure type [38]	
				Type II variation	New MA according to Article 8(3)
Abraxane	11/01/2008	paclitaxel	02/12/2013	X	
Ilaris[105]	23/10/2009	canakinumab	18/02/2013	X	
Invega	25/06/2007	paliperidone	08/04/2011	X	
Jinarc	27/05/2015	tolvaptan	See MA date		X
Lucentis	22/01/2007	ranibizumab	04/07/2013	X	
Ozurdex	27/07/2010	dexamethasone	16/06/2011	X	
Relistor	02/07/2008	methylnaltrexone bromide	27/05/2015	X	
Resolor	15/10/2009	prucalopride	27/05/2015	X	
Revlimid	14/06/2007	lenalidomide	13/06/2013	X	
Revolade	11/03/2010	eltrombopag	19/09/2013	X[106]	
RoActemra	16/01/2009	tocilizumab	01/08/2011	X	
Stivarga	26/08/2013	regorafenib	28/07/2014	X	
Torisel	19/11/2007	temsirolimus	14/10/2009	X	

[105] Approved under exceptional circumstances

[106] Included in a line extension

Name of	**MA date** [38]	**API** [38]	**Approval date of new indication"**	**Procedure type** [38]	
Votrient	14/06/2010	pazopanib	03/08/2012	X	
Xgeva	13/07/2011	denosumab	See MA date		X
Xiapex	28/02/2011	collagenase Clostridium histolyticum	30/01/2015	X	
Xtandi	21/06/2013	enzalutamide	28/11/2014	X	
Zytiga	05/09/2011	abiraterone	18/12/2012	X	

Table 8 MPs with PUMA

Name of the CAP	MA date [38]	API [38]	Legal Basis [38]	MAH [38]
Buccolam	05/09/2011	midazolam	Article 10(3)	ViroPharma SPRL
Hemangiol	23/04/2014	propranolol	Article 8(3)	Pierre Fabre Dermatologie

Table 9 OMPs with indications extended via type II variation

Name of the CAP	MA date [38]	API [38]	Legal basis [38]	ODD date (ODD no.) [38]	New indication(s) [38], falls within ...		Similarity assessment	MAH [38]
					... the existing ODD	... a separate ODD		
Arzerra[107]	19/04/2010	ofatumumab	Article 8(3)	07/11/2008	X [161]	-	-	Glaxo Group Ltd
Cayston	21/09/2009	aztreonam	Article 8(3)	21/06/2004	No information on discussion of OMP status provided in VAR			Gilead Sciences International Ltd.
Exjade[108]	28/08/2006	deferasirox	Article 8(3)	13/03/2002	X [162] [109]	-	-	Novartis Europharm Limited
Firazyr	11/07/2008	icatibant	Article 8(3)	17/02/2003	X [163]	-	-	Shire Orphan Therapies GmbH
Imbruvica	21/10/2014	ibrutinib	Article 8(3)	26/04/2012 (EU/3/12/984), 12/03/2013 (EU/3/13/1115), 29/04/2014 (EU/3/14/1264)	-	X [62] [110]	-	Janssen-Cilag International NV
Kalydeco	23/07/2012	ivacaftor	Article 8(3)	08/07/2008	X [164], [165]	-	-	Vertex Pharmaceuticals (U.K.) Ltd.

[107] Conditional approval

[108] 2 x extension of the indication via type II variation

[109] This refers to the 2nd extension of the indication, only.

[110] This refers to the ODD no. EU/3/14/1264.

Name of the CAP	**MA date** [38]	**API** [38]	**Legal basis** [38]	**ODD date (ODD no.)** [38]	**New indication(s)** [38]**, falls within ...**		**Similarity assessment**	**MAH** [38]
					... the existing ODD	**... a separate ODD**		
Kuvan	02/12/2008	sapropterin	Article 8(3)	08/06/2004	X [166]	-	-	Merck Serono Europe Ltd.
Myozyme	29/03/2006	alglucosidase alfa	VO EWG Nr. 2309/93	14/02/2001	No information on discussion of OMP status provided in VAR			Genzyme Europe B.V.
Nexavar[111]	19/07/2006	sorafenib	Article 8(3)	29/07/2004 (EU/3/04/207), 11/04/2006 (EU/3/06/364), 13/11/2013 (EU/3/13/1199, EU/3/13/1200)	-	X [167] [112]	-	Bayer Pharma AG
Revatio[113]	28/10/2005	sildenafil	VO EWG Nr. 2309/93	12/12/2003	-	-	X[114]	Pfizer Limited
Revlimid[115]	14/06/2007	lenalidomide	Article 8(3)	12/12/2003 (EU/3/03/177)	-	X [168] [116]	X[117]	Celgene Europe Ltd.

[111] 2 x extension of the indication via type II variation

[112] This refers to the ODD no. EU/3/13/1199 and no. EU/3/13/1200, and this refers to the 2nd extension of the indication, only.

[113] 2 x extension of the indication via type II variation

[114] 1. variation: “Revatio is considered as non-similar to Volibris and Tracleer” [66]; 2. variation: “This conclusion [on non-similarity] remains valid in the present application for an extension of indication” [66]

[115] 3 x extension of the indication via type II variation

Name of the CAP	MA date [38]	API [38]	Legal basis [38]	ODD date (ODD no.) [38]	New indication(s) [38], falls within ...		Similarity assessment	MAH [38]
					... the existing ODD	... a separate ODD		
				08/03/2004 (EU/3/04/192)				
Soliris[118]	20/06/2007	eculizumab	Article 8(3)	17/10/2003 (EU/3/03/166), 24/07/2009, (EU/3/09/653)	X [169], [170]	-	-	Alexion Europe SAS
Sprycel	20/11/2006	dasatinib	Article 8(3)	23/12/2005 (EU/3/05/339), 23/12/2005 (EU/3/05/338)	-	-	X[119]	Bristol-Myers Squibb Pharma EEIG
Tasigna	19/11/2007	nilotinib	Article 8(3)	22/05/2006	-	-	X[120]	Novartis Europharm Ltd.
Torisel	19/11/2007	temsirolimus	Article 8(3)	06/04/2006, (EU/3/06/365), 06/11/2006 (EU/3/06/420)	No information on discussion of OMP status provided in VAR			Pfizer Limited
Votubia[121]	02/09/2011	everolimus	Article 8(3)	04/08/2010	X [53]	-	-	Novartis Europharm Ltd.
Xagrid[122]	16/11/2004	anagrelide	VO EWG	29/12/2000	X [171]	-	-	Shire Pharmaceutical

[116] This refers to the ODD no. EU/3/04/192, and this refers to the 2nd extension of the indication, only.

[117] 1. variation: "Revlimid is not similar to Thalidomide Celgene" [172]; 3. variation: "Revlimid is not similar to Thalidomide Celgene neither to Imnovid" [173]

[118] 3 x extension of the indication via type II variation

[119] "The CHMP is of the opinion that Sprycel is not similar to Glivec and Tasigna". [64]

[120] "In addition, the CHMP […] considers Tasigna to be similar […] to Glivec for the same therapeutic indication. However, the [MAH] for Glivec has given his consent to the MAH" [67].

[121] Conditionally approved orphan MP

Name of the CAP	**MA date** [38]	**API** [38]	**Legal basis** [38]	**ODD date (ODD no.)** [38]	**New indication(s)** [38]**, falls within ...**		**Similarity assessment**	**MAH** [38]
					... the existing ODD	**... a separate ODD**		
			Nr. 2309/93					Contracts Ltd.
Zavesca[123]	20/11/2002	miglustat	VO EWG Nr. 2309/93	16/02/2006	No information on discussion of OMP status provided in VAR			Actelion Registration Ltd.

[122] Approved under exceptional circumstances

[123] 2 x extension of the indication via type II variation

Table 10 MPs with an extended SPC [155], [156], [157], [158], [159], [160]

Name of the CAP	MA date [38]	API [38]	MAH [38]
Abilify	04/06/2004	aripiprazole	Otsuka Pharmaceutical Europe Ltd
Baraclude	26/06/2006	entecavir	Bristol-Myers Squibb Pharma EEIG
Bridion	25/07/2008	sugammadex	Merck Sharp & Dohme Ltd
Cancidas	24/10/2001	caspofungin	Merck Sharp & Dohme Ltd
Cholestagel	10/03/2004	colesevelam	Genzyme Europe B.V.
Colobreathe	13/02/2012	colistimethate	Forest Laboratories UK Ltd
Enbrel	03/02/2000	etanercept	Pfizer Limited
Gardasil	20/09/2006	human papillomavirus type 6/11/16/18 L1 protein	Sanofi Pasteur MSD, SNC
Glivec	07/11/2001	imatinib	Novartis Europharm Ltd
Januvia	21/03/2007	sitagliptin	Merck Sharp & Dohme Ltd
Lantus	09/06/2000	insulin glargine	sanofi-aventis Deutschland GmbH
Orencia	21/05/2007	abatacept	Bristol-Myers Squibb Pharma EEIG
Plavix	15/07/1998	clopidogrel	Sanofi Clir SNC
Prezista	12/02/2007	darunavir	Janssen-Cilag International NV
Remicade	13/08/1999	infliximab	Janssen Biologics B.V.
Samsca	03/08/2009	tolvaptan	Otsuka Pharmaceutical Europe Ltd
Toujeo (previously Optisulin)	27/06/2000	insulin glargine	Sanofi-aventis Deutschland GmbH
Tracleer	15/05/2002	bosentan	Actelion Registration Ltd
Travatan	27/11/2001	travoprost	Alcon Laboratories (UK) Ltd
Vfend	19/03/2002	voriconazole	Pfizer Ltd
Viramune	05/02/1998	nevirapine	Boehringer Ingelheim International GmbH
Zometa	20/03/2001	zoledronic acid	Novartis Europharm Ltd

Table 11 Examples for MPs with indications extended via type II variation that are grouped with quality variations

Name of the CAP	API [38]	MA date [38]	Submission date of type II variation [38]	New indication [38]	Grouped variation
Eliquis	Apixaban (NAS)	18/05/2011	31/10/2013	"Treatment of [DVT] and [PE] and prevention of recurrent DVT and PE in adults"	Type IA_{IN} variation (class: B.II.e.5.a.1) "to add a pack size of 28 film-coated tablets" which is "associated with the new [...] indication" [174]
Humira	Adalimumab (NAS)	08/09/2003	Not specified (EC decision date: 18/03/2011)	Paediatric indication ("children below 13 years of age")	Several quality changes, e.g. to support the "flexible dosing with a single-use vial" [175], [176]
Ixiaro	Japanese-encephalitis virus (NAS)	31/03/2009	14/06/2012	paediatric indication	Type IA_{IN} variation (class B.II.e.6.a: "Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information") concerning the "modification of syringe label to include "half dose mark" for administration of a 0.25 ml nominal dose" for paediatric patients [177]
Sustiva	Efavirenz (NAS)	28/05/1999	17/01/2014	paediatric indication	Type IB variation to delete the superseded "oral solution pharmaceutical form" (class C.I.7.a) [56]

Name of the CAP	**API** [38]	**MA date** [38]	**Submission date of type II variation** [38]	**New indication** [38]	**Grouped variation**
				("children from 3 months of age to less than 3 years of age")	
Tamiflu	Oseltamivir (NAS)	20/06/2002	09/07/2014	Paediatric indication ("infants below one year of age")	Type IA_{IN} variation "that covers the addition of a 3 ml dispenser in the outer carton of Tamiflu 6 mg/ml, since it is considered a consequential change of the requested extension of indication in infants below 1 year of age to enable adequate dosing in this paediatric subgroup" [100]

Table 12 Examples for MPs with indications extended via type II variation, supported by new PD data

Name of the CAP	API [38]	MA date [38]	Initial indication [38]	Submission date of type II variation [38]	New indication [38]	New primary PD studies [38]		New clinical studies [38]
						In vitro	In vivo	
Votrient [178]	Pazopanib (NAS)	14/06/2010	1st line treatment of advanced RCC	07/07/2011	Treatment of patients with advanced STS	-	Mouse xenograft study on the effect of the API on growth of human liposarcoma[124]	Phase II study (supportive), Randomised, double-blind, placebo-controlled, multicenter Phase III study
Xiapex [69]	collagenase Clostridium histolyticum (NAS)	28/02/2011	Treatment of Dupuytren's contracture	12/06/2014	Treatment of adult men with Peyronie's disease	Study of the effect in "Peyronie's plaque tissue explants"	Study of the "collagenolytic effect [...] in Göttingen minipigs"	2x Phase I, 6x Phase II, 3x Phase III

[124] The CHMP noted that "the predictive value of mouse xenograft models for clinical efficacy is rather limited".

Table 13 MPs authorised after 01/01/2011 with indications extended via type II variation, affected by benefit assessment

Name of the CAP	MA date [38]	approval date of extended indication(s) [38]	Finished benefit assessment [148]	G-BA decision(s) [148]	Annual costs for the comparator € / patient according to module 1 [148]	Annual costs for the comparator € / patient [151]
Eliquis*	18/05/2011		15/06/2011	Not proven & minor	8.92 – 93.37	
		19/11/2012	01/01/2013	Minor	35.07 – 92.22 [125] / 11.22 [126]	12.45 – 144.95
		28/07/2014	01/09/2014	Minor & not proven	15.60 – 143.52	
Eviplera*	28/11/2011		15/01/2012	Minor	13,135	10,183
		29/11/2013	01/01/2014	Not proven	13,067 – 31,742[127]	5,382 – 16,905
Eylea*	22/11/2012		15/12/2012	Not proven	18,484 – 11,965	
		26/08/2013	01/10/2013	Not proven	0 – 14,421	
		06/08/2014	15/09/2014	Not proven	0 – 14,302	0 – 11,284
		24/02/2015	15/03/2015	Not proven	0 – 14,302	
		28/10/2015	Procedure ongoing[128]	Procedure ongoing	Not yet provided	
Fycompa*	23/07/2012		15/09/2012 & 15/05/2014[130]	Not proven	292 & 300 – 2,832	72 - 694
		22/06/2015[129]	-	-	-	-

[125] Indication „B“

[126] Indication „C“

[127] 1st year

[128] The decision is expected in mid of May 2016.

[129] The commercial distribution of Fycompa was terminated by the MAH upon the initial decision of the G-BA on the lack of additional benefit [152]. The new decision of the G-BA resulted in the same outcome. Therefore, it is assumed that the commercial distribution of Fycompa was not resumed which could be the reason that the extended indication was not submitted for benefit assessment.

Name of the CAP	**MA date** [38]	**approval date of extended indication(s)** [38]	**Finished benefit assessment** [148]	**G-BA decision(s)** [148]	**Annual costs for the comparator € / patient according to module 1** [148]	**Annual costs for the comparator € / patient** [151]
Gilenya*	17/03/2011	23/05/2014	15/04/2011 01/07/2014	Not proven (2x) & minor Not proven	17,173 – 18,496 20,202	13,042 – 14,742
Halaven*	17/03/2011	27/06/2014	01/05/2011 01/08/2014	Minor Moderate (1x) & not proven (2x)	299 – 11,394 2,193 – 45,425	1,468 – 26,977
Imbruvica* [131]	21/10/2014	03/07/2015	01/11/2014 Proceeding terminated[132]	Imbruvica -	n. a. (OMP) -	Not specified
Jakavi*	23/08/2012	11/03/2015	15/09/2012 & 15/05/2014[133] 15/04/2015	Minor & Moderate Moderate	0 – 4,879 & 3,323 – 22,507 513 – 14,775	Not specified
Kalydeco* [134]	23/07/2012	28/07/2014	15/08/2012 01/09/2014	Minor & Moderate Minor	12,672 21,782 – 31,667	Not specified
Komboglyze*	24/11/2011 [135]	24/10/2012 18/02/2013	15/11/2012 01/04/2013	Minor & not proven Not proven	66 - 806 684 - 812	24 - 837

[130] Repeated benefit assessment

[131] OMP

[132] The G-BA terminated the benefit assessment of the OMP Imbruvica because this MP reached the turnover limit of 50 million €. Therefore a full dossier needs to be submitted for benefit assessment (§ 35a(1) sentence 11 SGB V in conjunction with chapter 5 § 12 No. 2 VerfO).

[133] Exceeding of 50 million € turnover limit

[134] OMP

Name of the CAP	**MA date** [38]	**approval date of extended indication(s)** [38]	**Finished benefit assessment** [148]	**G-BA decision(s)** [148]	**Annual costs for the comparator € / patient according to module 1** [148]	**Annual costs for the comparator € / patient** [151]
Mekinist	30/06/2014	25/08/2015	17/03/2016	Not proven & Moderate	93,175 – 93,205	Not yet available
Opdivo	19/06/2015	28/10/2015	07/01/2016 04/02/2016	Moderate / Not proven Moderate / Not proven	4,370,632 – 111,496,562 0 – 126,341,980	Not yet available
Perjeta*	04/03/2013	28/07/2015	01/04/2013 ongoing	Moderate (1x) & not proven (2x) -	45,676 – 48,840 -	807 – 51,939 -
Stivarga*	26/08/2013	28/07/2014	01/10/2013 01/09/2014	Minor Not proven	1,669 – 20,598,948 -[136]	Not quantified
Tafinlar*	26/08/2013	25/08/2015	03/04/2014 17/03/2016	Not proven Moderate	72,089,080 130,445,632 – 130,487,324	73,613,45 Not yet available
Trajenta	24/08/2011	24/10/2012	01/10/2011 01/12/2012	Not proven Not proven	617 29- 784	3 - 886[137]
Tresiba*	21/01/2013	07/05/2014	01/05/2014 15/06/2014	Not proven Not proven	864 – 1,674 -[138]	316 - 687

[135] Komboglyze was initially marketed in Germany on 15/11/2012. Therefore the initial benefit assessment includes the 1st extension of indication of Komboglyze. (153)

[136] No dossier submitted

[137] Opt-out

[138] No dossier submitted

Name of the CAP	**MA date** [38]	**approval date of extended indication(s)** [38]	**Finished benefit assessment** [148]	**G-BA decision(s)** [148]	**Annual costs for the comparator € / patient according to module 1** [148]	**Annual costs for the comparator € / patient** [151]
		30/01/2015	01/03/2015	Not proven	1,224 – 1,813	
Xiapex	28/02/2011	30/01/2015	01/05/2011 -[139]	Not proven -	2,088 -	0 – 2,473[140]
Xtandi*	21/06/2013	28/11/2014	01/09/2013 01/01/2015	Moderate Moderate	0 1,470 – 51,855	249 – 41,765
Xultophy	18/09/2014	25/06/2015	01/05/2015 ongoing	Not proven -	659 – 1,673 659 – 1,243	-
Yervoy*	13/07/2011	31/10/2013	01/08/2011 15/12/2013	Moderate Not proven	4,725 6,330 – 131,601	4,089 – 74,622
Zytiga*	05/09/2011	18/12/2012	01/10/2011 15/01/2013	Moderate & not proven Moderate	4,753 – 22,495 3,759 – 6,832	17 – 19,817

*The reimbursement price is not published by the SHI.

[139] The MAH does not market Xiapex in Germany due to the G-BA's negative decision on the additional benefit [179].

[140] Opt-out

Table 14 MPs authorised before 01/01/2011 with indications extended via type II variation, affected by benefit assessment

Name of the CAP	MA date [38]	Approval date extensions of indication [38]	Finished benefit assessment [148]	G-BA decision(s) [148]
Eucreas	14/11/2007	25/10/2012	01/10/2013	Not proven
Galvus	26/09/2007	30/01/2012, 29/10/2012	01/10/2013 & 21/05/2015	Not proven
Jalra	19/11/2008	29/10/2012		
Xiliarx	19/11/2008	30/01/2012, 29/10/2012		
Icandra	01/12/2008	29/10/2012	01/10/2013	Not proven
Janumet, Velmetia	16/07/2008	02/06/2009, 28/10/2009	01/10/2013	Minor / Not proven
Januvia	21/03/2007	19/12/2007, 02/06/2009, 29/07/2009, 09/11/2009	01/10/2013	Minor / Not proven
Xelevia	21/03/2007	18/12/2007, 29/05/2009, 23/07/2009, 28/10/2009		
Nevanac	11/12/2007	22/12/2011	19/12/2013	Not proven
Onglyza	01/10/2009	22/11/2011, 18/02/2013 26/07/2013	01/10/2013 -	Minor / Not proven Procedure terminated on 17/04/2014[141]
Zomarist	01/12/2008	29/10/2012	01/10/2013	Not proven

[141] Due to the omission of article § 35a(6) SGB V

Hiermit erkläre ich an Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

München, den ___. Mai 2016

...…..……..…….

Silvia Balogh