

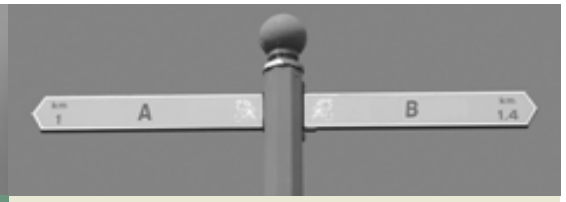

Faus & Moliner Abogados

Early access to medicinal products in Spain

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Spain's legal and administrative landscape

- Current political and economic environment.
- An administrative arena tough to navigate (Aemps, regions, hospitals, etc....).
- The constitutional dimension of the issue. Characterization of the right to healthcare protection.

Compassionate use: Definition

- Use of a product prior to any approval.
- A MAA must exist ot the product must be undergoing clinical trials.
- Only for chronic diseases or seriously debilitating illness or one that is considered life-threatening.
- No valid approved alternative.

Compassionate use: Approval

- Requires approval by AEMPS.
- MA applicant or CT Sponsor must agree to deliver product.
- Informed consent from patient.
- Approval may be for single or multiple use.

Compassionate use: AEMPS role

- Manages approvals.
- Should foster inclusion of patients in CT when possible.
- Reports adverse events to MA applicant or CT Sponsor.
- Liaison with EU and regional authorities.

Compassionate use: HCP/Site role

- Secure informed consent.
- Justify need for use of the product, with special focus on why the patient may not be treated with an alternative approved product.
- Approves application to Aemps.
- Reports adverse events.

Compassionate use: MAA/Sponsor role

- Collaborate with Aemps to define terms for multiple use.
- Immediate report of any safety concern.
- Confirm availability of product.
- Supply not need to be for free (at least for the time being).

Off label use: Definition and basic terms

- Use of a product under terms different from SmPC.
- No valid approved alternative.
- Informed consent and proper record in clinical file history.
- The procotol of the healthcare centre or of the regional authorities must be followed



Off label use: Relevance of informed consent

- Information must be exhaustive, clear, comprehensible and adequate, including benefits, risks, etc...

- Always in written form (¿?) (surgery operations, invasive treatments or those who may generate foreseable risks).

Off label use: Protocols

- Tool to manage pharma expenditure in some cases.
- Must not impose systematic use of a non-approved drug if an approved product exists for a given indication.
- Civil, administrative and criminal liabilities may affect the administration, the hospital managers and doctors.

Off label use: Approvals

- No approval from Aemps required.
- Originally, only from HCP.
- After Royal Decree-Law 16/2012 : Committees responsible for therapeutical protocols or the equivalent body in each region.

Off label use: Case law

- If approved alternatives exist, off label is a breach of lex artis.
- Compliance with the law overrides any medical interest because the objective of the law is to secure the safety of the patient.



Early Access: Definition and basic terms

- Product approved elsewhere not yet available in Spain.
- EMA approved products, prior to pricing and reimbursement procedures being completed in Spain.
- No valid available alternative.

Early access: A common situation in Spain

Brand	INN	Company	EMA	Ind.
Thalidomide Celgene	thalidomide	Celgene Europe Limited	16/04/2008	cancer
Ceplene	histamine dihydrochloride	Meda AB	07/10/2008	cancer
Firdapse	amifampridine	BioMarin Europe Ltd	23/12/2009	non cancer
Plenadren	hydrocortisone	Shire Services BVBA	03/11/2011	non cancer
Xaluprine	6-mercaptopurine monohydrate	Nova Laboratories Ltd	09/03/2012	cancer
Bronchitol	mannitol	Pharmaxis Pharmaceuticals Ltd	13/04/2012	non cancer
Revestive	teduglutide	NPS Pharma Holdings Ltd	30/08/2012	non cancer
Glybera	alipogene tiparvovec	uniQure biopharma B.V.	25/10/2012	non cancer
Bosulif	bosutinib (as monohydrate)	Pfizer Ltd	27/03/2013	cancer
Iclusig	ponatinib	Ariad Pharma Ltd	01/07/2013	non cancer
Sirturo	bedaquiline fumarate	Janssen-Cilag International N.V.	05/03/2014	non cancer
Cometriq	cabozantinib	TMC Pharma Services Ltd	21/03/2014	cancer
Granupas	para-aminosalicylic acid	Lucane Pharma	07/04/2014	non cancer
Vimizim	recombinant human n-acetylgalactosamine-6-sulfatase (rhgalns)	BioMarin Europe Ltd	28/04/2014	non cancer
Translarna	ataluren	PTC Therapeutics Int Ltd	31/07/2014	non cancer

Early access: A common situation in Spain

Brand	INN	Company	EMA	Ind.
Cerdelga	**eliglustat**	**Genzyme Europe BV**	**19/01/2015**	**non cancer**
Holoclar	autologous human corneal epithelial cells containing stem cells	Chiesi Farmaceutici S.p.A.	17/02/2015	cancer
Lenvima	**lenvatinib mesylate**	**Eisai Europe Ltd**	**28/05/2015**	**cancer**
Farydak	panobinostat lactate anhydrous	Novartis Europharm Ltd	28/08/2015	cancer
Kanuma	**sebelipase alfa**	**Alexion Europe SAS**	**28/08/2015**	**non cancer**
Strensiq	asfotase alfa	Alexion Europe SAS	28/08/2015	non cancer
Cresemba	**isavuconazole**	**Basilea Medical Ltd**	**15/10/2015**	**non cancer**
Kyprolis	carfilzomib	Amgen Europe B.V.	19/11/2015	cancer
Blincyto	**blinatumomab**	**Amgen Europe B.V.**	**23/11/2015**	**cancer**
Wakix	pitolisant	Bioprojet Pharma	31/03/2016	non cancer
Idelvion	**albutrepenonacog alfa**	**CSL Behring GmbH**	**11/05/2016**	**cancer**
Alprolix	eftrenonacog alfa	Biogen Idec Ltd - SOBI	12/05/2016	non cancer
Darzalex	**daratumumab**	**Janssen-Cilag Intl. N.V.**	**20/05/2016**	**cancer**
Galafold	migalastat hydrochloride	Amicus Therapeutics UK Ltd	26/05/2016	non cancer

Early Access: Approval

- Requires approval by AEMPS.
- HCP / Hospital sends request, assessment to be completed in 3 months (otherwise, positive silence).
- Informed consent from patient.
- Approval may be for single or multiple use.

Early Access: HCP/Site role

- Secure informed consent.
- Justify need for use of the product and medical assessment. Need to explain units required and duration of treatment.
- Product not to be used off-label unless MA holder approves.
- Reports adverse events.

Early access: Tips on MAH role (1/3)

- Unavoidable situation in a connected world.
- Triggers contact with stakeholders.
- Creates messaging and focus on individual cases (patients & associations).
- Be prudent, may be perceived as undue pressure on P&R authorities.

Early access: Tips on MAH role (2/3)

- Be careful re promotion (cfr. answering individual requests)
- Involve local KOL's in the design and implementation.
- Presentation to authorities carefully selected together with KOL's.

Early access: Tips on MAH role (3/3)

- Be ready to concede on some economic aspects.
- Risk-sharing schemes are unavoidable nowadays in Spain.
- The value of clinical trials vs. clinical practice.
- A payment by result scheme seems the most probable option.

A look into future developments:

- New regulations on P&R may tend to avoid preassure resulting from Early Access Programs.
- MOH and regions likely to play some role given impact on hospital expenditure.
- Pre-P&R price approval for early access (or free supplies).
- Concern about anti-trust cases (abuse).



Thank you for your attention

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