



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/498952/2015

European Medicines Agency decision CW/0001/2015

of 23 July 2015

on class waivers, in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

Only the English text is authentic.



European Medicines Agency decision

CW/0001/2015

of 23 July 2015

on class waivers, in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

The European Medicines Agency,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004¹,

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency²,

Having regard to the decision of the European Medicines Agency P/60/2008 of 8 September 2008, P/63/2010 of 26 April 2010, P/345/2010 of 20 December 2010 and decision CW/1/2011 of 19 December 2011,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued of its own motion on 17 July 2015 in accordance with Article 12 and Article 14(2) of Regulation (EC) No 1901/2006,

Having regard to Article 25 of Regulation (EC) No 1901/2006,

Whereas:

- (1) The Paediatric Committee of the European Medicines Agency has adopted an opinion of its own motion for a review of the class waivers.
- (2) It is therefore appropriate to adopt a decision reviewing the class waivers.

¹ OJ L 378, 27.12.2006, p.1.

² OJ L 136, 30.4.2004, p. 1.

Has adopted this decision:

Article 1

A review of the granted class waivers, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency attached hereto in Annex I, together with its appendices, is hereby agreed.

Article 2

This decision applies to the production of the information referred to in Article 7(1) of Regulation (EC) No 1901/2006.

Article 3

Without prejudice to the agreement to confirm the waivers set forth in paragraph (4) of the opinion of the PDCO annexed hereto, the decisions P/60/2008, P/63/2010, P/345/2010 and CW/1/2011 of the European Medicines Agency respectively adopted on 8 September 2008, 26 April 2010, 20 December 2010 and 19 December 2011 are hereby repealed.

Article 4

This decision shall enter into force on 27 July 2015. The requirements set out in Articles 7 and 8 of Regulation (EC) No 1901/2006 shall not apply for the revoked class waivers set forth in Annex I of the Opinion for 36 months from the date of this Decision, in accordance with Article 14(3) of Regulation (EC) No 1901/2006. The same shall apply to the revised class waivers in Annex I of the Opinion.

Done at London, 23 July 2015

For the European Medicines Agency
Jordi Llinares Garcia
Head of Division (ad interim)
Human Medicines Research and Development Support
(Signature on file)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/PDCO/664578/2012
Human Medicines Research and Development Support Division

Opinion of the Paediatric Committee on the review of the list of class waivers

Basis for opinion

Having regard to Article 14(2) of Regulation (EC) No 1901/2006,

Having regard to the decisions of the European Medicines Agency P/60/2008 of 8 September 2008, P/63/2010 of 26 April 2010, P/345/2010 of 20 December 2010 and CW/1/2011 of 19 December 2011,

the Paediatric Committee started a procedure to review the list of class waivers on 3 October 2012.

Opinion

Pursuant to Article 14(2) of Regulation (EC) No 1901/2006, the Paediatric Committee adopted the following opinion:

(1) to revoke, pursuant to Article 14(3) of Regulation (EC) No 1901/2006 and in accordance with Annex I of this Opinion, the waivers for:

- all medicines for treatment of liver and intrahepatic bile duct carcinoma;
- all medicines for treatment of kidney and renal pelvis carcinoma;
- all medicines for treatment of coronary atherosclerosis, peripheral atherosclerosis, vascular dementia and vascular cognitive disorder / impairment;
- all medicines for the treatment of Parkinson disease (non-juvenile);
- all medicines for treatment of Huntington chorea;
- all medicines for treatment of amyotrophic lateral sclerosis;

on the ground that the concerned condition does occur in the paediatric population(s), and clinical studies may fulfil a therapeutic need of the paediatric population;



(2) to revise waivers included in Decisions P/63/2010, P/345/2010 and CW/1/2011 pursuant to Article 12 of Regulation (EC) No 1901/2006 and in accordance with Annex I of this Opinion. The revised waivers are:

- the classes of androgen receptor modulator, of oestrogen receptor modulator, of growth and sex hormone as well as their releasing or inhibiting factors, and of sex hormone-metabolism modulator medicinal products for treatment of breast malignant neoplasms,¹ prostate malignant neoplasms² and neuroendocrine malignant neoplasms;³
- the class of first-generation taxoid medicinal products for treatment of breast malignant neoplasms, gynaecological epithelial malignant neoplasms,⁴ prostate malignant neoplasms, intestinal malignant neoplasms,⁵ pancreatic malignant neoplasms, head and neck epithelial malignant neoplasms⁶ as well as lung malignant neoplasms;⁷
- the class of Ecteinascidin medicinal products for treatment of gynaecological epithelial malignant neoplasms;
- the class of Her- / Epidermal growth factor-receptor antibody medicinal products for treatment of breast malignant neoplasms, intestinal malignant neoplasms and head and neck epithelial malignant neoplasms;
- the class of thymidylate synthase inhibitor medicinal products for the treatment of intestinal malignant neoplasms and lung malignant neoplasms;

on the ground that these classes of medicinal products are likely to be ineffective in all of the paediatric population in the concerned condition, in accordance with Article 11.1 of said Regulation;

(3) to revise the waivers included in Decisions P/63/2010, P/345/2010 and CW/1/2011 pursuant to Article 12 of Regulation (EC) No 1901/2006 and in accordance with Annex I of this Opinion. The revised waivers are:

- the class of Colchicum alkaloids (colchicine and its derivatives) medicinal products for the treatment of primary gout;⁸
- the class of androgen antagonist medicinal products for treatment of benign prostatic hyperplasia;
- the class of pyrimidine- and pyrimidine analogue-containing medicinal products for treatment of breast malignant neoplasms, intestinal malignant neoplasms, lung malignant neoplasms, pancreatic malignant neoplasms,⁹ head and neck epithelial malignant neoplasms, skin malignant neoplasms¹⁰ and actinic keratosis;
- the class of first- and second generation platinum-containing medicinal products for treatment of urinary tract malignant neoplasms,¹¹ head and neck epithelial malignant neoplasms and lung malignant neoplasms;

¹ Previously listed: breast carcinoma

² Previously listed: prostate carcinoma

³ Previously listed: gastroenteropancreatic neuroendocrine tumours, gastric carcinoids

⁴ Previously listed: Fallopian tube carcinoma, cervix and corpus uteri carcinoma, endometrial carcinoma, vaginal and vulvar carcinoma, peritoneal carcinoma

⁵ Previously listed: adenocarcinoma of the colon and rectum, gastric adenocarcinoma

⁶ Previously listed: oropharyngeal, laryngeal or nasal epithelial carcinoma

⁷ Previously listed: lung carcinoma (small cell and non-small cell carcinoma)

⁸ Previously listed: primary gout

⁹ Previously listed: adenocarcinoma of the pancreas

¹⁰ Previously listed: melanoma (from 0 to less than 12 years old), basal cell carcinoma

¹¹ Previously listed: ureter and bladder carcinoma

- the class of alkylating-methylating medicinal products for treatment of skin malignant neoplasms;
- the class of ribonucleotide reductase beta-2 inhibitor medicinal products for treatment of myeloproliferative neoplasms;¹²
- the class of primarily alkylating medicinal products for treatment of myeloproliferative neoplasms and mature B, T and NK cell neoplasms;¹³
- the class of photosensitising medicinal products for treatment of head and neck epithelial malignant neoplasms;
- the class of retinoic X receptor-activating medicinal products for treatment of mature B, T and NK cell neoplasms;
- the class of immunomodulatory cytokine medicinal products for treatment of neuroendocrine malignant neoplasms, skin malignant neoplasms, myeloproliferative neoplasms and mature B, T and NK cell neoplasms;

on the ground that the classes of medicinal products do not represent a significant therapeutic benefit over existing treatments for paediatric patients in the concerned condition, in accordance with Article 11.1 of said Regulation;

(4) to confirm the following waivers granted by Decisions P/60/2008, P/63/2010, P/345/2010 and CW/1/2011 and to include them in this Opinion:

- the class of peroxisome proliferator-activated receptor (PPAR)-gamma modulators, including dual and multiple PPAR modulator medicinal products (e.g., thiazolidinediones, glitazars, triple modulators) for treatment of type II diabetes mellitus;
- all classes of medicinal products for treatment of primary and secondary osteoarthritis;
- all classes of medicinal products for treatment of organic amnesic syndrome (excluding amnesic syndrome caused by alcohol and other psychoactive substances);
- all classes of medicinal products for treatment of age-related macular degeneration and diabetic macular oedema;
- all classes of medicinal products for treatment of climacteric symptoms associated with decreased oestrogen levels, as occurring at menopause;
- all classes of medicinal products for treatment of Alzheimer's disease;
- all classes of medicinal products for treatment of erectile dysfunction;
- all classes of medicinal products for treatment of chronic obstructive pulmonary disease (COPD) (excluding chronic lung diseases associated with long-term airflow limitation, such as asthma, bronchopulmonary dysplasia, primary cilia dyskinesia, obstructive lung disease related to graft-versus-host disease after [bone-marrow] transplantation);
- all classes of medicinal products for treatment of vulvar intraepithelial neoplasia.

¹² Previously listed: primary myelofibrosis

¹³ Previously listed: hairy cell leukaemia, multiple myeloma, chronic lymphocytic leukaemia, follicular lymphoma

A consolidated list of class waivers on conditions or group of conditions and classes of medicinal products adopted by the Paediatric Committee is in Annex II.

The Norwegian Paediatric Committee member agrees with the above-mentioned recommendation of the Paediatric Committee.

This opinion is forwarded to the Deputy Executive Director of the European Medicines Agency.

London, 17 July 2015

Annex I - Scientific discussion

Waivers previously granted in Decisions P/63/2010, P/345/2010 and CW/1/2011 shall be reviewed in accordance with Article 14 of Regulation (EC) No. 1901/2006 taking into account the new information on the diseases affecting the paediatric population and the related medicinal products or classes of medicinal products. Previously granted class waivers, above-mentioned, did not sufficiently rely on the characteristics of medicinal products or classes of medicinal products. For the present review, all available scientific evidence were taken into account by the Paediatric Committee (PDCO), including the data generated since the granting of the previous class-waiver decision(s) and the knowledge acquired with some medicinal products or some classes of medicinal products. The assessment of all the available data in support of the reviewed class-waiver has integrated the characteristics of a medicinal product or a class of medicinal products according to article 11 of Regulation (EC) No 1901/2006, which is reflected in the scope of the reviewed class-waivers and refers to specific medicinal products or classes of medicinal products. Where scientifically relevant, the PDCO has also recommended the granting of a waiver for a group of conditions when justified by the available scientific data, the characteristics of the diseases and the medicinal product or a class of medicinal products.

I.1. Revoked waivers

The Paediatric Committee assessed scientific literature and other publicly available data as part of the review of the list of class waivers. In the following, the data summarised concern the paediatric population (from birth to less than 18 years of age) and became available after the class waiver had been granted.

I.1.1. Liver and intrahepatic bile duct carcinoma

The Paediatric Committee noted that recent data indicated that at least 200 paediatric patients per year are diagnosed with liver cancer in the European Union based on cancer registry statistics (International Agency for Research on Cancer 2012). Liver carcinoma, a subtype of liver cancer, represents about 30% (table 1 in Siegel et al. 2014) of all liver cancers in children. In children of school age and adolescents, it occurs in an adult-like setting of chronic cirrhosis or inflammation, or in an otherwise healthy liver. The more common subtype of liver cancer in children, hepatoblastoma, occurs at a median age of about 2 years and its incidence is reported to increase, possibly related to increases of low-birth weight and prematurely born children. Features of both liver carcinoma and hepatoblastoma are found in the subtype of transitional cell tumours of the liver, which is reported to occur between 5 and 15 years of age in children (Rodriguez-Galindo et al. 2013).

The Committee concluded that cancers of the liver affect the paediatric population, although much less frequently than in adults, and are life-threatening diseases that represent unmet therapeutic needs of children. As a consequence, the Committee recommended the revocation of the waiver for all medicines for treatment of liver and intrahepatic bile duct carcinoma.

I.1.2. Kidney and renal pelvis carcinoma

The Paediatric Committee took note of recent data indicating that about 900 paediatric patients per year are diagnosed with kidney (renal) cancer in the European Union based on cancer registry statistics (International Agency for Research on Cancer 2012), and with an increasing incidence (Pastore et al. 2006; Siegel et al. 2014). The most frequent renal cancer in children is a subtype called Wilms tumour or nephroblastoma (Pastore et al. 2006), while the second most frequent subtype is renal cell carcinoma (Siegel et al. 2014, fig.1). The latter subtype is well-characterised in paediatric

patients and includes translocation-related renal cell carcinoma (Geller et al. 2015), which also occurs in adults.

The Committee concluded that kidney cancers affect the paediatric population, even though much less frequently than in adults, and are quickly deteriorating, life-threatening diseases that represent unmet therapeutic needs of children (see also Spreafico 2015). As a consequence, the Committee recommended the revocation of the waiver for all medicines for treatment of kidney and renal pelvis carcinoma.

1.1.3. Coronary atherosclerosis, peripheral atherosclerosis, vascular dementia and vascular cognitive disorder / impairment

Data accumulated over recent years from interventional and non-interventional studies indicate that atherosclerosis (blood vessel wall inflammation) already develops in the paediatric population, as evidenced by increased intima-media thickness, arterial stiffness and endothelial dysfunction (Cote et al. 2013; Rodrigues et al. 2013) in different blood vessel systems (e.g., vessels of the heart, the extremities or the brain). In cells that line blood vessels, fatty acids continuously pile up. Over time, this leads to the formation of fat plaques (atheroma) that can be seen under the microscope. A first medical consequence, some of the blood vessel functions are impaired, which can be detected already early in childhood. With increasing age, plaques grow in size and can break up more often. At such an event, the material that is set free from the plaque can block the blood from flowing into some heart or brain vessels, leading to infarcts in these organs. Hence vascular dementia and some vascular cognitive disorder / impairment are late complications of atherosclerosis.

Atherosclerosis occurs for example in children with a fatty acid metabolism disorder, children who had Kawasaki disease, children who have a nephrotic syndrome, children who are treated with anti-epilepsy medicines or children who received radiation therapy or obese children.

The Paediatric Committee noted the lack of prevalence estimates for atherosclerosis in children, beyond figures known for fatty acid metabolism disorders. The Committee concluded that atherosclerosis occurs in children and represents unmet needs of the paediatric population in terms of prevention as well as treatment. As a consequence, the Committee recommended the revocation of the waiver for all medicines for treatment of coronary atherosclerosis, peripheral atherosclerosis, vascular dementia and vascular cognitive disorder / impairment.

1.1.4. Parkinson disease (non-juvenile)

According to recent data, specific forms of Parkinson disease occur in the paediatric population (Thomsen & Rodnitzky 2010). "Juvenile" Parkinsonism is well described and only defined by its occurrence in patients of less than 21 years of age. Affected paediatric patients present with clinical features that are similar to idiopathic Parkinson's disease or manifest parkinsonism in adults. The treatment of affected children is also similar to that of Parkinson disease in adults.

The Paediatric Committee concluded that Parkinson disease is a rare, disabling disorder that affects the paediatric population and that has infrequently been studied in children, while it represents specific and unmet therapeutic paediatric needs. As a consequence, the Committee recommended the revocation of the waiver for all medicines for the treatment of Parkinson disease (non-juvenile).

1.1.5. Huntington chorea

According to recent data (Roos 2011), Huntington disease may occur in the paediatric population in a juvenile form. It is reported to be about 6% of the cases of Huntington disease (which itself has a

prevalence of 1/10,000) and is characterised in paediatric and adult populations by a similar molecular aberration in the *HTT* (huntingtin) gene.

The Paediatric Committee concluded that Huntington chorea is a rare disorder in the paediatric that has infrequently been studied in children, but it represents specific and unmet therapeutic paediatric needs. As a consequence, the Committee recommended the revocation of the waiver for all medicines for treatment of Huntington chorea.

1.1.6. Amyotrophic lateral sclerosis

Recent publications on new genetic findings in motor neuron disease have extended previous knowledge on juvenile amyotrophic lateral sclerosis (Orban et al. 2007): Sporadic and familial forms of motor neuron diseases as well as different mutations are now all recognised to present with overlapping phenotypes and clinical similarities (Finsterer & Burgunder 2014), so that there is no criterion other than age to distinguish juvenile from adult onset forms. The diagnosis of juvenile amyotrophic lateral sclerosis is made based on clinical findings; it is a very rare disease in children occurring at a mean age of 6.5 years (Bertini 2014).

The Paediatric Committee noted that such disabling disorders are rare and have infrequently been studied in children; however they represent specific and unmet paediatric therapeutic needs. As a consequence, the Committee recommended the revocation of the waiver for all medicines for treatment of amyotrophic lateral sclerosis.

I.2. Revised waivers

I.2.1. Medicinal products that are likely to be ineffective in the paediatric population

A number of classes of medicinal products have been studied as anti-cancer treatments in the paediatric population and / or in paediatric disease models. Consequently, based on the available paediatric data the PDCO considered that further studies could not be expected to be justified in children with the diseases stated in the below table. The Committee considered that the pharmacological profiles of the active substances that were studied are sufficiently similar to allow extending these conclusions to the respective classes of medicinal products. These conclusions would not prevent to consider studies if there are new, strong scientific findings.

The Paediatric Committee assessed the available data and used the expertise of its members to form the conclusion that the classes of medicinal products listed in the table (below) and used in the group of conditions mentioned in the table do not have relevant anti-cancer activity in children and thus that there is no relevant paediatric use in the diseases stated in the below table. Therefore, requirements for paediatric studies in the diseases stated in the below table should be waived for these classes of medicinal products on the ground that they are likely to be ineffective in children, in whom the medicines have been studied based on the current understanding of their pharmacological properties and use in adults. The concerned classes of medicinal products are therefore specified in the waiver for the conditions or group of conditions as stated below.

| Class of medicinal product | References | Group of conditions where the medicinal product is authorised for treatment |
|---|--|---|
| Androgen receptor modulator, oestrogen receptor modulator, growth and sex hormone as well as their releasing or inhibiting factors, sex hormone-metabolism modulator medicinal products ¹⁴ | (Bourdeaut et al. 2009) (Janem et al. 2010) (Skapek et al. 2013) (Michalski et al. 2010) | <ul style="list-style-type: none"> • Breast malignant neoplasms • Prostate malignant neoplasms • Neuroendocrine malignant neoplasms |
| First-generation taxoid medicinal products ¹⁵ | (Horton et al. 2008) (Norwegian Medicines Agency 2010) (Sanofi 2012) (Jacobs et al. 2010) | <ul style="list-style-type: none"> • Breast malignant neoplasms • Gynaecological epithelial malignant neoplasms • Prostate malignant neoplasms • Intestinal malignant neoplasms • Head and neck epithelial malignant neoplasms • Lung malignant neoplasms • Pancreatic malignant neoplasms |

¹⁴ Examples: Tamoxifen, Toremifene, Fulvestrant, Degarelix, Enzalutamide, Abiraterone, Somatostatin, Octreotide

¹⁵ Examples: Paclitaxel, Docetaxel, Ixabepilone

| Class of medicinal product | References | Group of conditions where the medicinal product is authorised for treatment |
|---|---|--|
| Her-/Epidermal growth factor-receptor antibody medicinal products ¹⁶ | (Trippett et al. 2009) (Ebb et al. 2012) (European Medicines Agency 2009) | <ul style="list-style-type: none"> • Breast malignant neoplasms • Intestinal malignant neoplasms • Head and neck epithelial malignant neoplasms |
| Ecteinascidin medicinal products | (Baruchel et al. 2012) (European Medicines Agency 2014) | <ul style="list-style-type: none"> • Gynaecological epithelial malignant neoplasms |
| Thymidylate synthase inhibitor medicinal product ¹⁷ | (Warwick et al. 2013) (Horton et al. 2005) (Malempati et al. 2007) | <ul style="list-style-type: none"> • Intestinal malignant neoplasms • Lung malignant neoplasms |

1.2.2. Medicinal products that lack significant therapeutic benefit over existing treatments for paediatric population

For a number of classes of medicinal products, studies for treatment of various conditions in the paediatric population are available. Medicinal products are subsequently used or authorised for paediatric medical care in some of the studied conditions stated in the below table. The Paediatric Committee therefore considered that further studies in the diseases stated in the below table could not be expected to be justified in the paediatric population with the classes of medicines stated in this table. The profiles of active substances used for treatment in these diseases were considered by the Committee to be sufficiently similar to allow extending these conclusions to classes of medicinal products. This conclusion would not prevent to consider studies if there are new scientific findings.

The PDCO assessed the available data and used the expertise of its members to form the conclusion that for the classes of medicinal products listed (below) requirements to agree a paediatric investigation plan with the Committee and to perform accordingly paediatric studies in the diseases stated in the below table should be waived for medicinal products in these classes on the grounds that they do not represent a significant therapeutic benefit over existing treatments for paediatric patients. The concerned classes of medicinal products are therefore specified in the waiver for the conditions or group of conditions as stated below.

¹⁶ Examples: Trastuzumab, Pertuzumab

¹⁷ Examples: Pemetrexed, Raltitrexed

| Class of medicinal product | Reference(s) | Group of conditions where the medicinal product is used for the treatment of |
|---|---|---|
| Pyrimidine- and pyrimidine analogue-containing medicinal products ¹⁸ | (Kilburn et al. 2013) (Hoffmann-La Roche 2014) (Trobaugh-Lotrario & Katzenstein 2012) (Buehrlen et al. 2012) | <ul style="list-style-type: none"> • Breast malignant neoplasms • Intestinal malignant neoplasms • Head and neck epithelial malignant neoplasms • Lung malignant neoplasms • Pancreatic malignant neoplasms • Skin malignant neoplasms • Actinic keratosis |
| First- and second-generation platinum-containing medicinal products ¹⁹ | (Pizzo & Poplack 2011, p.301) | <ul style="list-style-type: none"> • Urinary tract malignant neoplasms • Intestinal malignant neoplasms • Head and neck epithelial malignant neoplasms • Lung malignant neoplasms |
| Immunomodulatory cytokine medicinal products ²⁰ | (Buehrlen et al. 2012) | <ul style="list-style-type: none"> • Neuroendocrine malignant neoplasms • Skin malignant neoplasms • Myeloproliferative neoplasms • Mature B, T and NK cell neoplasms • Neuroblastoma |
| Photosensitising medicinal products | (Basset-Seguin et al. 2014) | <ul style="list-style-type: none"> • Head and neck epithelial malignant neoplasms |
| Colchicum alkaloids (colchicine and its derivatives) | (Medicines & Healthcare products Regulatory Agency (MHRA) 2012) (Kallinich et al. 2007) | <ul style="list-style-type: none"> • Primary gout • Auto-inflammatory syndromes |

¹⁸ Examples: 5-Fluorouracil, Capecitabine

¹⁹ Examples: Cisplatin, carboplatin, oxaliplatin

²⁰ Examples: Interleukin 2, Interferon alpha

| Class of medicinal product | Reference(s) | Group of conditions where the medicinal product is used for the treatment of |
|--|--|---|
| Alkylating-methylating medicinal products ²¹ | (Pizzo & Poplack 2011, pp.304, 649, 290) | <ul style="list-style-type: none"> • Skin malignant neoplasms • Brain tumours • Neuroblastoma • Sarcoma • Hodgkin lymphoma |
| Androgen antagonists ²² | (Speiser et al. 2010) | <ul style="list-style-type: none"> • Benign prostatic hyperplasia • Congenital adrenal hyperplasia • Hyperandrogenism |
| Ribonucleotide reductase beta-2 inhibitor medicinal products ²³ | (Sharma et al. 2014, sec.O–079) (Pizzo & Poplack 2011, p 621) | <ul style="list-style-type: none"> • Myeloproliferative neoplasms • Leukaemia |
| Primarily alkylating medicinal products | (Pizzo & Poplack 2011, pp 290 and 299) (Michel et al. 2011) | <ul style="list-style-type: none"> • Myeloproliferative neoplasms • Mature B, T and NK cell neoplasms • Hodgkin lymphoma |
| Retinoic X receptor-activating medicinal products ²⁴ | (Mehta et al. 2012) | <ul style="list-style-type: none"> • Mature B, T and NK cell neoplasms |

²¹ Examples: Dacarbazine (DTIC), Temozolomide

²² Example: Finasteride

²³ Example: Hydroxycarbamide (hydroxyurea)

²⁴ Examples: Bendamustine, Carmustine (BCNU); Temoporfin; Bexarotene

Annex II - Consolidated list of class waivers on conditions or group of conditions and classes of medicinal products

1. the classes of androgen receptor modulator, of oestrogen receptor modulator, of growth and sex hormone as well as their releasing or inhibiting factors, and of sex hormone-metabolism modulator medicinal products for treatment of breast malignant neoplasms, prostate malignant neoplasms and neuroendocrine malignant neoplasms;
2. the class of first-generation taxoid medicinal products for treatment of breast malignant neoplasms, gynaecological epithelial malignant neoplasms, prostate malignant neoplasms, intestinal malignant neoplasms, pancreatic malignant neoplasms, head and neck epithelial malignant neoplasms as well as lung malignant neoplasms;
3. the class of Ecteinascidin medicinal products for treatment of gynaecological epithelial malignant neoplasms;
4. the class of Her- / epidermal growth factor-receptor antibody medicinal products for treatment of breast malignant neoplasms, intestinal malignant neoplasms and head and neck epithelial malignant neoplasms;
5. the class of thymidylate synthase inhibitor medicinal products for the treatment of intestinal malignant neoplasms and lung malignant neoplasms;
6. the class of Colchicum alkaloids (colchicine and its derivatives) medicinal products for the treatment of primary gout;
7. the class of androgen antagonist medicinal products for treatment of benign prostatic hyperplasia;
8. the class of pyrimidine- and pyrimidine analogue-containing medicinal products for treatment of breast malignant neoplasms, intestinal malignant neoplasms, lung malignant neoplasms, pancreatic malignant neoplasms, head and neck epithelial malignant neoplasms, skin malignant neoplasms and actinic keratosis;
9. the class of first- and second-generation platinum-containing medicinal products for treatment of urinary tract malignant neoplasms, head and neck epithelial malignant neoplasms and lung malignant neoplasms;
10. the class of alkylating-methylating medicinal products for treatment of skin malignant neoplasms;
11. the class of ribonucleotide reductase-beta-2 inhibitor medicinal products for treatment of myeloproliferative neoplasms;
12. the class of primarily alkylating medicinal products for treatment of myeloproliferative neoplasms and mature B, T and NK cell neoplasms;
13. the class of photosensitising medicinal products for treatment of head and neck epithelial malignant neoplasms;
14. the class of retinoic X receptor-activating medicinal products for treatment of mature B, T and NK cell neoplasms;
15. the class of immunomodulatory cytokine medicinal products for treatment of neuroendocrine malignant neoplasms, skin malignant neoplasms, myeloproliferative neoplasms and mature B, T and NK cell neoplasms;

16. the class of peroxisome proliferator-activated receptor (PPAR)-gamma modulators, including dual and multiple PPAR modulator (e.g., thiazolidinediones, glitazars, triple modulators) medicinal products for treatment of type II diabetes mellitus;
17. all classes of medicinal products for treatment of primary and secondary osteoarthritis;
18. all classes of medicinal products for treatment of organic amnesic syndrome (excluding amnesic syndrome caused by alcohol and other psychoactive substances);
19. all classes of medicinal products for treatment of age-related macular degeneration and diabetic macular oedema;
20. all classes of medicinal products for treatment of climacteric symptoms associated with decreased oestrogen levels, as occurring at menopause;
21. all classes of medicinal products for treatment of Alzheimer's disease;
22. all classes of medicinal products for treatment of erectile dysfunction;
23. all classes of medicinal products for treatment of chronic obstructive pulmonary disease (COPD) (excluding chronic lung diseases associated with long-term airflow limitation, such as asthma, bronchopulmonary dysplasia, primary cilia dyskinesia, obstructive lung disease related to graft-versus-host disease after [bone-marrow] transplantation);
24. all classes of medicinal products for treatment of vulvar intraepithelial neoplasia.

References

- Baruchel, S. et al., 2012. A phase 2 trial of trabectedin in children with recurrent rhabdomyosarcoma, Ewing sarcoma and non-rhabdomyosarcoma soft tissue sarcomas: a report from the Children's Oncology Group. *European Journal of Cancer (Oxford, England: 1990)*, 48(4), pp.579–585.
- Basset-Seguín, N. et al., 2014. Consensus recommendations for the treatment of basal cell carcinomas in Gorlin syndrome with topical methylaminolaevulinate-photodynamic therapy. *Journal of the European Academy of Dermatology and Venereology: JEADV*, 28(5), pp.626–632.
- Bertini, E., 2014. Orphanet: Juvenile amyotrophic lateral sclerosis. Available at: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=300605 [Accessed November 21, 2014].
- Bourdeaut, F. et al., 2009. VIP hypersecretion as primary or secondary syndrome in neuroblastoma: A retrospective study by the Société Française des Cancers de l'Enfant (SFCE). *Pediatric Blood & Cancer*, 52(5), pp.585–590. Available at: <http://onlinelibrary.wiley.com/doi/10.1002/pbc.21912/abstract> [Accessed November 25, 2014].
- Buehrlen, M. et al., 2012. Multimodal treatment, including interferon beta, of nasopharyngeal carcinoma in children and young adults: preliminary results from the prospective, multicenter study NPC-2003-GPOH/DCOG. *Cancer*, 118(19), pp.4892–4900.
- Cote, A.T. et al., 2013. Childhood obesity and cardiovascular dysfunction. *Journal of the American College of Cardiology*, 62(15), pp.1309–1319.
- Ebb, D. et al., 2012. Phase II Trial of Trastuzumab in Combination With Cytotoxic Chemotherapy for Treatment of Metastatic Osteosarcoma With Human Epidermal Growth Factor Receptor 2 Overexpression: A Report From the Children's Oncology Group. *Journal of Clinical Oncology*, 30(20), pp.2545–2551. Available at: <http://jco.ascopubs.org/content/30/20/2545> [Accessed June 4, 2013].
- European Medicines Agency, 2009. European Medicines Agency - Human medicines - Withdrawn applications - Theraloc. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000931/wapp/Initial_authorisation/human_wapp_000043.jsp&mid=WC0b01ac058001d128&source=homeMedSearch&category=human [Accessed November 25, 2014].
- European Medicines Agency, 2014. Summary of product characteristics - European public assessment report - Yondelis. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000773/human_med_001165.jsp&mid=WC0b01ac058001d124 [Accessed April 19, 2015].
- Finsterer, J. & Burgunder, J.-M., 2014. Recent progress in the genetics of motor neuron disease. *European Journal of Medical Genetics*, 57(2-3), pp.103–112.
- Geller, J.I. et al., 2015. Characterization of adolescent and pediatric renal cell carcinoma: A report from the Children's Oncology Group study AREN03B2. *Cancer*, 121(14), pp.2457–2464. Available at: <http://onlinelibrary.wiley.com/doi/10.1002/cncr.29368/abstract> [Accessed July 16, 2015].
- Hoffmann-La Roche, 2014. A Study of Capecitabine (Xeloda) and Concomitant Radiation Therapy in Children With Newly Diagnosed Brainstem Gliomas - Full Text View - ClinicalTrials.gov. Available at: <http://clinicaltrials.gov/ct2/show/study/NCT01118377> [Accessed November 25, 2014].
- Horton, T.M. et al., 2008. A Phase 1 and pharmacokinetic clinical trial of paclitaxel for the treatment of refractory leukemia in children: a Children's Oncology Group study. *Pediatric Blood & Cancer*, 50(4), pp.788–792.

- Horton, T.M. et al., 2005. Phase I trial and pharmacokinetic study of raltitrexed in children with recurrent or refractory leukemia: a pediatric oncology group study. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, 11(5), pp.1884–1889.
- International Agency for Research on Cancer, 2012. GLOBOCAN 2012 age-specific table. Available at: http://globocan.iarc.fr/old/age-specific_table_n.asp?selection=63990&title=European+Union+%28EU-28%29&sex=0&type=0&stat=1&window=1&sort=0&submit=%C2%A0Execute%C2%A0 [Accessed November 25, 2014].
- Jacobs, S. et al., 2010. Phase II trial of ixabepilone administered daily for five days in children and young adults with refractory solid tumors: a report from the children's oncology group. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, 16(2), pp.750–754.
- Janem, W. et al., 2010. Malignant insulinoma in a child. *Pediatric Blood & Cancer*, 55(7), pp.1423–1426. Available at: <http://onlinelibrary.wiley.com/doi/10.1002/pbc.22784/abstract> [Accessed November 25, 2014].
- Kallinich, T. et al., 2007. Colchicine Use in Children and Adolescents With Familial Mediterranean Fever: Literature Review and Consensus Statement. *Pediatrics*, 119(2), pp.e474–e483. Available at: <http://pediatrics.aappublications.org/content/119/2/e474> [Accessed November 26, 2014].
- Kilburn, L.B. et al., 2013. Phase I trial of capecitabine rapidly disintegrating tablets and concomitant radiation therapy in children with newly diagnosed brainstem gliomas and high-grade gliomas. *Neuro-Oncology*, 15(6), pp.759–766.
- Malempati, S. et al., 2007. Phase I trial and pharmacokinetic study of pemetrexed in children with refractory solid tumors: the Children's Oncology Group. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 25(12), pp.1505–1511.
- Medicines & Healthcare products Regulatory Agency (MHRA), 2012. Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended COLCHICINE UK/W/015/pdWS/001. Available at: http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Paediatric_Regulation/Assessment_Reports/Article_45_work-sharing/Colchicine_2012_02_45_PdAR.pdf [Accessed April 22, 2015].
- Mehta, N. et al., 2012. Bexarotene is active against subcutaneous panniculitis-like T-cell lymphoma in adult and pediatric populations. *Clinical Lymphoma, Myeloma & Leukemia*, 12(1), pp.20–25.
- Michalski, A. et al., 2010. The addition of high-dose tamoxifen to standard radiotherapy does not improve the survival of patients with diffuse intrinsic pontine glioma. *Journal of Neuro-Oncology*, 100(1), pp.81–88.
- Michel, G. et al., 2011. Weight-based strategy of dose administration in children using intravenous busulfan: Clinical and pharmacokinetic results. *Pediatric Blood & Cancer*. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21254374> [Accessed January 25, 2011].
- Norwegian Medicines Agency, 2010. Taxol Paclitaxel - Rapporteur's Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No. 1901/2006. Available at: http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Paediatric_Regulation/Assessment_Reports/Article_45_work-sharing/Paclitaxel_2010_04_45PaedPdAR.pdf [Accessed November 25, 2014].
- Orban, P. et al., 2007. Chapter 15 Juvenile amyotrophic lateral sclerosis. *Handbook of Clinical Neurology*, 82, pp.301–312.
- Pastore, G. et al., 2006. Malignant renal tumours incidence and survival in European children (1978-1997): report from the Automated Childhood Cancer Information System project. *European Journal of Cancer (Oxford, England: 1990)*, 42(13), pp.2103–2114.

- Pizzo, P. & Poplack, D., 2011. *Principles and Practice of Pediatric Oncology* 6th ed., Philadelphia: Lippincott Williams & Wilkins.
- Rodrigues, A.N. et al., 2013. Cardiovascular risk factor investigation: a pediatric issue. *International Journal of General Medicine*, 6, pp.57–66.
- Rodriguez-Galindo, C. et al., 2013. Children's Oncology Group's 2013 blueprint for research: Rare tumors. *Pediatric Blood & Cancer*, 60(6), pp.1016–1021. Available at: <http://onlinelibrary.wiley.com/doi/10.1002/pbc.24428/abstract> [Accessed April 19, 2015].
- Roos, R., 2011. Juvenile Huntington disease. Available at: http://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=19562 [Accessed October 24, 2014].
- Sanofi, 2012. Docetaxel in Combination With Cisplatin-5-fluorouracil for the Induction Treatment of Nasopharyngeal Carcinoma in Children and Adolescents - Full Text View - ClinicalTrials.gov. Available at: <http://clinicaltrials.gov/ct2/show/NCT00565448> [Accessed November 25, 2014].
- Sharma, M. et al., 2014. To compare role of hydroxyurea and hyperhydration versus hyperhydration alone to decrease total leukocyte count in children of acute leukemia with hyperleukocytosis: a randomized control trial [abstract O-079]. In *Pediatric Blood & Cancer*. pp. S105–S433. Available at: <http://onlinelibrary.wiley.com/doi/10.1002/pbc.25314/abstract> [Accessed November 25, 2014].
- Siegel, D.A. et al., 2014. Cancer Incidence Rates and Trends Among Children and Adolescents in the United States, 2001–2009. *Pediatrics*, 134(4), pp.e945–e955. Available at: <http://pediatrics.aappublications.org/content/134/4/e945> [Accessed October 23, 2014].
- Skapek, S.X. et al., 2013. Safety and efficacy of high-dose tamoxifen and sulindac for desmoid tumor in children: results of a Children's Oncology Group (COG) phase II study. *Pediatric Blood & Cancer*, 60(7), pp.1108–1112.
- Speiser, P.W. et al., 2010. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology and Metabolism*, 95(9), pp.4133–4160. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2936060/> [Accessed April 22, 2015].
- Spreafico, F., 2015. Paediatrics: Towards evidence-based management of paediatric RCC. *Nature Reviews Urology*, advance online publication. Available at: <http://www.nature.com/nrurol/journal/vaop/ncurrent/full/nrurol.2015.158.html#access> [Accessed July 16, 2015].
- Thomsen, T.R. & Rodnitzky, R.L., 2010. Juvenile parkinsonism: epidemiology, diagnosis and treatment. *CNS drugs*, 24(6), pp.467–477.
- Trippett, T.M. et al., 2009. Phase I and Pharmacokinetic Study of Cetuximab and Irinotecan in Children With Refractory Solid Tumors: A Study of the Pediatric Oncology Experimental Therapeutic Investigators' Consortium. *Journal of Clinical Oncology*, 27(30), pp.5102–5108. Available at: <http://jco.ascopubs.org/content/27/30/5102> [Accessed May 19, 2014].
- Trobaugh-Lotrario, A.D. & Katzenstein, H.M., 2012. Chemotherapeutic approaches for newly diagnosed hepatoblastoma: past, present, and future strategies. *Pediatric Blood & Cancer*, 59(5), pp.809–812.
- Warwick, A.B. et al., 2013. Phase 2 Trial of Pemetrexed in Children and Adolescents with Refractory Solid Tumors: a Children's Oncology Group Study. *Pediatric blood & cancer*, 60(2), pp.237–241. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3463652/> [Accessed April 22, 2015].