



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Human Medicines Research and Development Support Division

## EMA/PDCO Summary Report on the review of the list of granted Class Waivers



## 1. Administrative and procedure information

<b>Procedure event</b>	<b>Date</b>
PDCO discussion and draft Opinion	16 January 2015
Stakeholder consultation	11 May 2015
PDCO discussion and Opinion adopted	17 July 2015

## 2. Background

The review and update of waivers (of medicine development for children<sup>1</sup>) is a task of the Paediatric Committee (PDCO) at the European Medicines Agency, as per Article 14 of Regulation (EC) No 1901/2006 (the "Paediatric Regulation"). The primary aim of this Regulation is to facilitate the development and accessibility of medicinal products for the paediatric population, by offering support for paediatric medicine development, including where this development has not been considered by the pharmaceutical sector.

In this regard, recital 8 of the said regulation states that

*"The Paediatric Committee should be primarily responsible for the scientific assessment and agreement of paediatric investigation plans and for the system of waivers and deferrals thereof; it should also be central to various support measures contained in this Regulation. In its work, the Paediatric Committee should consider the potential significant therapeutic benefits for the paediatric patients involved in the studies or the paediatric population at large including the need to avoid unnecessary studies."*

In line with the recital 8 and Article 6 of the Paediatric Regulation, the tasks of the PDCO comprise, amongst others, the scientific review of any potential benefit of a specific medicinal product for paediatric populations, thereby promoting to address therapeutic needs in children which have not been met. Conversely, a paediatric development can be waived by the PDCO for instance to avoid unnecessary studies in paediatric patients.

Currently, most of the class waivers refer only to a medical disease (condition) and thus they could be used by pharmaceutical companies developing in a condition subject to a class waiver, without regard for their medicinal products developed in this condition. The class waiver Decision is published on the EMA website and can be used to comply with legal requirements of the Paediatric Regulation when medicinal products are proposed for adults only. Therefore, for the conditions included in the list of class waivers, no separate product-specific application for a waiver is required on this occasion.

Following the experience acquired from the adoption of the Paediatric Regulation, the PDCO noted the current list of class waiver has led to difficulties for the PDCO to maintain a balance of supportive measures, of potential benefit considerations and of measures to avoid unnecessary studies. Findings include that there were insufficient opportunities for the PDCO to consider the potential benefits of individual medicinal products for the paediatric population at large. The PDCO also noticed that new medicines with unprecedented benefits in terms of efficacy in life-threatening diseases were developed and proposed for adults only (for example, Masters et al. 2015). These new medicines presented completely novel pharmacological properties, and their medical plausibility in the range of conditions relevant for the paediatric population could not be reviewed.

This was also obvious to paediatric patient representatives and academic stakeholders (Adamson PC 2013; Institute of Cancer Research 2014; Vassal et al. 2013). They raised repeatedly the issue that a number of medicinal products likely have significant benefit for children; indeed, these medicinal products could not be scientifically reviewed by the PDCO. The situation led to increasing concerns about how to serve public health objectives in paediatric populations with a high burden of disease.

The PDCO, as part of its regular review of the list of class waivers in accordance with Article 14(2) and 14(3), has decided to update the list of class of waivers taking into account the available information data at the time of the review. A summary of the scientific discussion is presented below. The PDCO adopted its Opinion on the review of the class waiver list after consulting stakeholders from the pharmaceutical sector and taking into account their comments.

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<sup>1</sup> In this document, the term "children" is used as a synonym for the totality of the paediatric population.

### **3. Scientific discussion and assessment of new data**

#### ***Class waivers recommended to be revoked***

##### **Liver and intrahepatic bile duct carcinoma**

The Paediatric Committee took note of recent data indicating 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.

##### **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.

##### **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.

### **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).

### **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.

### **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.

## ***Waivers recommended to be revised***

Previously granted waivers need to be reviewed in accordance with Article 14 of Regulation (EC) No 1901/2006 to take due account of new information on some diseases affecting the paediatric population and their related medicinal products or classes of medicinal products.

Most previously granted waivers were not focused on the characteristics of medicinal products or classes of medicinal products.

For the present review, together with the review of all available evidence, in particular data generated since the granting of the previous class-waiver decision(s), the Paediatric Committee took into consideration the knowledge acquired on some medicinal products or some classes of medicinal products to update the class-waivers.

The assessment of all available data in support of the reviewed class waiver has led to incorporate the characteristics of a medicinal product or a class of medicinal products in the class waiver for the concerned condition. Subsequently, the scope of the reviewed class waiver refers to specific medicinal products or classes of medicinal products.

Where scientifically relevant, the Committee recommended the granting of a waiver for a defined group of conditions (when justified by the available data, the characteristics of the diseases and the medicinal product or a class of medicinal products).

The following sections address diseases in the class waiver list for which relevant new paediatric information has been found. With the objective to comprehensively address each disease, all classes of medicinal products are reviewed where medicines are recommended in treatment guidelines or are authorised in the European Union for the treatment of the respective disease. A number of these medicinal products have been used as treatments in studies with paediatric patients or in other types of studies, or have been reviewed for their potential for paediatric use.

Informative publications were selected from results of searches for paediatric studies in Medline via PubMed (using terms of the active substance, "clinical trial" or "review" as publication types, "children" and "neoplasm" as MeSH terms), in public trial registries, in assessments reports for procedures under Articles 45 and 46 of the Paediatric Regulation, in the Pediatric Blood & Cancer journal, in SIOP congress abstracts and in EMA assessments of paediatric needs.

For each class of medicinal products, a brief summary of the publicly available evidence is provided, followed by scientific conclusions from a paediatric perspective and with recommended action(s) on the list of class waivers. Schematic and tabulated overviews are provided at the end.

### **Breast carcinoma**

For the medical treatment of breast carcinoma, (a) endocrine therapy, (b) chemotherapy / targeted therapy, (c) HER2-directed therapy and (d) bone-directed therapy are mentioned in recent guidelines.<sup>2</sup> For these types of medical treatments, medicines from one or more classes are authorised for the treatment of breast carcinoma,<sup>3</sup> including (a) bazedoxifene, fulvestrant, raloxifene, tamoxifen, toremifene, (b) bevacizumab, capecitabine, docetaxel, doxorubicin, eribulin, everolimus, paclitaxel, (c) lapatinib, pertuzumab, trastuzumab, trastuzumab emtansine and (d) ibandronic acid. The review applies to the group of conditions of breast malignant neoplasms, notably all subtypes of breast carcinoma / cancer.

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<sup>2</sup> <http://www.esmo.org/Guidelines/Breast-Cancer>

<sup>3</sup> Centrally authorised medicinal products:  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Fanding%2Fepar\\_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=breast&keywordSearch=Submit&searchType=ti&taxonomyPath=&treeNumber=&searchGenericType=generics](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Fanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=breast&keywordSearch=Submit&searchType=ti&taxonomyPath=&treeNumber=&searchGenericType=generics)

### ***Discussion of medicines used in adults with a breast carcinoma, as investigated in paediatric conditions***

For (a) endocrine therapy for treatment of breast carcinoma, medicines are used that work in different, but quite similar ways (oestrogen receptor modulators, sex hormones releasing or inhibiting factors or sex hormone-metabolism modulators). As the mechanisms of action are closely related, these classes of medicinal products were considered together. A study was conducted in 59 paediatric patients with desmoid fibromatosis, a locally-aggressive, intermediate soft tissue tumour type (Skapek et al. 2013). The treatment with tamoxifen, a non-steroidal oestrogen receptor antagonist, and with sulindac was reported to have shown little effect on the size of the tumour (tumour response) and on the survival time until tumour progression (progression-free survival). The addition of tamoxifen to radiation therapy was studied in 31 paediatric patients with a diffuse-intrinsic pontine glioma, a rare, highly-malignant tumour of the brain stem; progression free survival is reported to have been worse compared with historical data and overall survival was not improved (Michalski et al. 2010). According to a review of anti-cancer medicines (Vassal 2009), fulvestrant, an oestrogen receptor down-regulator, has “no rationale for other diseases in children” (that is, other than the cancer for which it is authorised in adults). The medicines used in these studies were considered representative of the classes of oestrogen receptor modulators, sex hormones releasing or inhibiting factors or sex hormone-metabolism modulators. The available paediatric data were considered to lack signals of interesting anti-tumour activity, such as significant proportion and extent of tumour shrinkage or significant improvement in the balance of survival to the burden of disease and treatment, in the paediatric conditions.

Regarding (b) chemotherapy for treatment of breast carcinoma, authorised medicines belong to several different classes of mechanisms of medicinal products. Docetaxel and paclitaxel were the first taxane-based medicinal products to be marketed and these are referred to as the class of first-generation taxoid medicinal products (Muggia & Kudlowitz 2014), for which paediatric studies were reviewed. A controlled trial of docetaxel in 75 patients from 9 to 21 years of age as add-on to induction chemotherapy for nasopharyngeal carcinoma is reported with no differences in the complete response rate (Sanofi 2012). The regulatory assessment of paediatric studies of paclitaxel included four phase 1 and two phase 2 studies, with in total 147 children with a malignant disease (Norwegian Medicines Agency 2010). The results did not support further development of paclitaxel as treatment of brain tumours, neuroblastoma or acute lymphoblastic leukaemia, even though some children with a solid malignant tumour responded and further studies could be considered. In a trial of single-agent paclitaxel in 63 children with an advanced leukaemia, 4 objective responses were found in 54 evaluable patients (Horton et al. 2008). The phase 2 trial of single-agent ixabepilone, an unauthorised medicine that works by microtubule-stabilisation similar to taxoids, in 61 children and young adults with a refractory solid malignant tumour did not show clinical evidence of anti-tumour activity (Jacobs et al. 2010). On this basis, first-generation taxoids were considered to lack signals of interesting anti-tumour activity in the studied paediatric diseases.

Paediatric studies with bevacizumab, eribulin and everolimus are ongoing and paediatric investigation plans have been agreed for these medicinal products; while doxorubicin is used to treat neoplasms in children and some doxorubicin-containing medicinal products are authorised for certain paediatric uses, paediatric studies are ongoing and some needs for further paediatric studies may exist. For these medicines, therefore, no conclusions concerning a waiver can be drawn at this time.

Capecitabine belongs to the class of pyrimidine- and pyrimidine analogue-containing medicinal products together with fluorouracil and tegafur / gimeracil / oteracil (and gemcitabine, authorised for pancreatic malignant neoplasm, discussed in a subsequent section). Capecitabine as add-on to scheduled radiation therapy was studied for dose-finding in 24 paediatric and young adult patients with a newly-diagnosed brain tumour (Kilburn et al. 2013); capecitabine at the recommended dose added

to radiation therapy was then studied in 44 paediatric patients with a newly-diagnosed brain stem tumour, in whom a single objective response, a median progression-free survival time of 5 months and a median overall survival time of 10 months have been publicly provided (Hoffmann-La Roche 2014). These results, even though only limited details are available, do not seem different from historical results with radiation therapy (Jansen et al. 2012; Hargrave et al. 2006). A detailed discussion of 13 paediatric studies with more than 1300 children with hepatoblastoma, including more than 280 children who had been administered 5-fluorouracil, partly in controlled trials, has been published (Trobaugh-Lotrario & Katzenstein 2012); however, a treatment effect of 5-fluorouracil could not be defined in this publication. A report of a non-controlled study of 45 children and young adults with a nasopharyngeal carcinoma, which is a rare paediatric malignant neoplasm, included that a multimodal therapy including 5-fluorouracil resulted in complete remission in almost all patients at the end of therapy and in an event-free survival rate of 92% after a median observation time of 30 months (Buehrle et al. 2012). Taken together with a previously available report (Rodriguez-Galindo et al. 2005), it is understood that 5-fluorouracil is an established part of the treatment administered as part of the medical care of children with nasopharyngeal carcinoma, whereas for capecitabine, no paediatric use is apparent. Given the weight of the existing paediatric data in the studied malignancies, it was considered that further studies with pyrimidine- and pyrimidine analogue-containing medicinal products may not be needed in the paediatric population.

Regarding the class of (c) Her- / Epidermal growth factor-receptor antibody medicinal products for treatment of breast carcinoma, paediatric studies that were reviewed included a trial of trastuzumab as add-on to chemotherapy in 41 patients (14 years mean age) with a metastatic Her2 overexpressed osteosarcoma (Ebb et al. 2012); a therapeutic benefit remained uncertain and outcome was poor. A study of cetuximab (authorised for treatment of intestinal and head and neck epithelial malignant carcinoma, discussed in a subsequent section) in combination with irinotecan in 46 children with a refractory solid malignant tumour (not selected for biological characteristics) documented only 2 partial responses (Trippett et al. 2009). Based on the main study of the nimotuzumab development, involving 47 children and adolescents with glioma, the Committee for medicinal products for human use (CHMP) had concerns that benefits had not been demonstrated, as this study did not show a benefit in terms of survival and none of the patients treated with nimotuzumab showed a complete disappearance of the tumours (European Medicines Agency 2009). Taken together, Her- / epidermal growth factor-receptor antibody medicinal products lack signals of relevant anti-tumour activity in the studied paediatric diseases.

Regarding (d) bone-directed therapy, no relevant paediatric data could be reviewed; therefore, conclusions concerning a waiver cannot be drawn for this class of medicinal products at this time.

### ***Discussion of the concerned condition subject to the class waiver***

There are no paediatric data showing that the above-mentioned classes of medicinal products (oestrogen receptor modulators, sex hormones releasing or inhibiting factors or sex hormone-metabolism modulators, first-generation taxoid medicinal products, pyrimidine- and pyrimidine analogue-containing medicinal products as well as Her- / epidermal growth factor-receptor antibody medicinal products) are safe and effective for treatment of breast carcinoma, and no such data will be available.

The existing paediatric data indicate that the classes of medicinal products of oestrogen receptor modulators, sex hormones releasing or inhibiting factors or sex hormone-metabolism modulators, first-generation taxoid medicinal products and Her- / epidermal growth factor-receptor antibody medicinal products are likely ineffective in the paediatric population with the studied malignancies. Requirements for paediatric studies should be waived for these classes of medicinal products in the concerned condition. This waiver should not apply when any of these classes of medicinal products are proposed



for treatment of other diseases. Unprecedented pharmacological properties in these classes of medicinal products, and unprecedented therapeutic situations in the disease, should lead to a specific evaluation of any recommendation to fulfil unmet needs or to ascertain significant therapeutic benefits in the paediatric population.

The existing paediatric data for pyrimidine- and pyrimidine analogue-containing medicinal products are used as a basis of evidence for treatment of paediatric patients. Requirements for further paediatric studies should hence be waived for this class of medicinal products in the concerned condition. To require paediatric studies may not be justified by expected therapeutic benefit. This waiver should not apply when these classes of medicinal products are proposed for treatment of other diseases.

## **Prostate carcinoma**

For the medical treatment of prostate carcinoma, (a) endocrine therapy, (b) chemotherapy, (c) particle-emitting medicines and (d) bone-directed therapy are mentioned in recent guidelines.<sup>4</sup> For these types of medical treatments, medicines from one or more classes of medicinal products are authorised in the European Union for the treatment of prostate carcinoma,<sup>5</sup> including (a) abiraterone, dagarelix, enzalutamide, (b) cabazitaxel, docetaxel, (c) <sup>223</sup>Radium and (d) denosumab. In order to be inclusive, the review covers the group of conditions of prostate malignant neoplasms, notably prostate carcinoma.

### ***Discussion of medicines used in adults with a prostate carcinoma, as investigated in paediatric conditions***

Regarding (a) endocrine therapy, this includes the classes of androgen receptor modulators, of sex hormones as well as their releasing or inhibiting factors, and of sex hormone-metabolism modulator medicinal products. No paediatric data in addition to those reviewed in the preceding section (breast carcinoma) could be retrieved for review.

Regarding (b) chemotherapy, this includes the class of first-generation taxoid medicinal products; the review of the paediatric data for this class of medicinal product is in the preceding section.

Regarding (c) particle-emitting therapy and (d) bone-directed therapy, no relevant paediatric data could be retrieved for review.

### ***Discussion of the concerned condition subject to the class waiver***

There are no paediatric data showing that the above-mentioned classes of medicinal products (androgen receptor modulators, oestrogen receptor modulators, growth and sex hormones as well as their releasing or inhibiting factors, sex hormone-metabolism modulator medicinal products, first-generation taxoid medicinal products) are safe and effective for treatment of prostate carcinoma, and no such data will be available.

The existing paediatric data however indicate that the classes of medicinal products of oestrogen receptor modulators, sex hormones releasing or inhibiting factors or sex hormone-metabolism modulators and first-generation taxoids are likely ineffective in the paediatric population with the studied malignancies. Requirements for paediatric studies should be waived for these classes of medicinal products in the concerned condition. This waiver should not apply when any of these classes

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<sup>4</sup> <http://www.esmo.org/Guidelines/Genitourinary-Cancers/Prostate-Cancer>

<sup>5</sup> Centrally authorised medicinal products:  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar\\_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=prostate&keywordSearch=Submit&searchType=ti&taxonomyPath=&treeNumber=&searchGenericType=generics](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=prostate&keywordSearch=Submit&searchType=ti&taxonomyPath=&treeNumber=&searchGenericType=generics)

of medicinal products are proposed for treatment of other diseases. Unprecedented pharmacological properties in these classes of medicinal products, and unprecedented therapeutic situations in the disease, should lead to a specific evaluation of any recommendation to fulfil unmet needs or to ascertain significant therapeutic benefits in the paediatric population.

## **Ureter and bladder carcinoma**

For the medical treatment of such diseases, cytotoxic chemotherapy using (a) a platinum-containing medicine in combination with (b) medicines such as anti-metabolites, vinca alkaloids and anthracyclines are mentioned in recent guidelines.<sup>6</sup> For patients who are deemed unfit to well tolerate cisplatin, carboplatin is mentioned, a second-generation platinum compound. Authorised medicines from these classes of medicinal products include (a) cisplatin, carboplatin and (b) gemcitabine, methotrexate, vinflunine and doxorubicin. The carcinomas of the ureter and bladder are included in the group of urinary tract malignant neoplasms, to which this review applies.

### ***Discussion of medicines used in adults with an urinary tract malignant neoplasm, as investigated in paediatric conditions***

With respect to (a), a large number of reports of paediatric studies of first- and second-generation platinum compounds can be found. A first regulatory assessment (MEB The Netherlands & MPA Sweden 2006) included only two paediatric trials and no recommendations for paediatric use could be made. Subsequently, results of some more completed paediatric studies have been submitted,<sup>7</sup> which however appear to be a fraction of existing paediatric data. Larger meta-analyses of paediatric studies of platinum compounds with respect to pharmacokinetics, safety and efficacy seem to be lacking. There may be some remaining uncertainties about the safety (allergic reactions, hearing impairment occur possibly more often in children than adults) and about the dosing (related to variability between patients and in a given patient); the dosing may however be optimised using therapeutic drug monitoring approaches (for example, Veal et al. 2007). According to paediatric oncology literature (Pizzo & Poplack 2011, p.301), cisplatin is an effective medicine for treatment of testicular tumours in children and is also known to be active against osteosarcoma, neuroblastoma, Wilms tumour, other germ cell tumours and brain tumours; where carboplatin is described to be active against brain tumours, neuroblastoma, sarcomas and germ cell tumours. Meanwhile, for some cisplatin products authorised in Europe, posologies for paediatric use have been added to the Summary of Product characteristics, for treatment of paediatric patients with a testicular tumour.

Regarding the different classes of medicinal products referred to in (b), paediatric studies are ongoing with medicines belonging to these classes and hence no conclusions can be drawn at this time.

### ***Discussion of the concerned condition subject to the class waiver***

There are no paediatric data showing that first- and second-generation platinum compounds are safe and effective for treatment of ureter and bladder carcinoma, and no such data will be available. Taken together, given the amount of existing paediatric data, first- and second-generation platinum compounds are known to be used for treatment of paediatric patients. Requirements for further studies with first- and second-generation platinum compounds should be waived for this class of medicinal products in the concerned condition. To require paediatric studies may not be justified by expected therapeutic benefit. This waiver should not apply when these classes of medicinal products are proposed for treatment of other diseases.

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<sup>6</sup> <http://www.esmo.org/Guidelines/Genitourinary-Cancers/Bladder-Cancer>

<sup>7</sup> [http://art45-paediatric-studies.ema.europa.eu/clinicaltrials/search\\_results.php?Category=&Active\\_substance\\_INN=carboplatin&cTitle=&Therapeutic\\_area\\_MESH\\_terms=&Scope\\_of\\_the\\_study=&ATC\\_Code=&cBrands=&Clinical+Trials\\_submit=Submit](http://art45-paediatric-studies.ema.europa.eu/clinicaltrials/search_results.php?Category=&Active_substance_INN=carboplatin&cTitle=&Therapeutic_area_MESH_terms=&Scope_of_the_study=&ATC_Code=&cBrands=&Clinical+Trials_submit=Submit)

## **Gastroenteropancreatic neuroendocrine tumours and gastric carcinoids**

In order to be inclusive, the review applies to the group of conditions of neuroendocrine malignant neoplasms, which encompasses diseases such as gastroenteropancreatic neuroendocrine tumours and gastric carcinoids, as well as other malignant carcinoid tumours with features of carcinoid syndrome, malignant VIPomas and glucagonomas, because these share certain pathological and medical characteristics. For the medical treatment of such diseases, (a) somatostatin therapy, (b) cytokine therapy, (c) targeted anti-cancer medicines, (d) chemotherapy and (e) peptide receptor-targeted radiation therapy are mentioned in recent guidelines.<sup>8</sup> For these types of medical treatments, medicines from one or more classes of medicinal products are authorised in the European Union for the treatment of such disease, including (a) octreotide, lanreotide, (b) interferon alpha-2b, (c) everolimus, sunitinib and (e) <sup>90</sup>Yttrium.

### ***Discussion of medicines used in adults with a neuroendocrine malignant neoplasm, as investigated in paediatric conditions***

Regarding (a) somatostatin therapy for neuroendocrine malignant diseases, this growth hormone release inhibitor is considered a type of endocrine therapy, related to those reviewed above. A review of 22 paediatric patients with a neuroblastic tumour producing VIP found that all patients required surgical removal in order to achieve control of the tumour and symptoms, whereas it is discussed that failure of somatostatin treatment given to a single patient is consistent with previous reports and that such failure discourages using somatostatin as effective surgical treatment might be delayed (Bourdeaut et al. 2009). The case of a paediatric patient with a metastatic insulinoma that did not respond to octreotide is reported together with a summary of 9 previously reported paediatric patients, two of whom had been treated with octreotide, with variable results, suggesting that management of this disease is challenging (Janem et al. 2010). Considering somatostatin (a growth hormone release inhibitor) together with endocrine therapies discussed above (section on breast carcinoma), there seems no relevant anti-tumour activity in the paediatric diseases studied for the classes of androgen receptor modulators, oestrogen receptor modulators, growth and sex hormones as well as their releasing or inhibiting factors, sex hormone-metabolism modulator medicinal products.

Regarding (b) immunomodulatory cytokine therapy, paediatric studies with the class of immunomodulatory medicinal products are discussed in the section on skin malignant neoplasms (below) as also medicines other than interferon were studied in children; the conclusions based on the paediatric data for this class of medicinal products however apply as per the discussion below.

Regarding (c) targeted anti-cancer medicines, these encompass several classes of medicinal products with which paediatric studies are ongoing and therefore, no conclusions can be drawn at this time.

Regarding (d) chemotherapy, this includes first-generation taxoids, and the review of the relevant paediatric data for this class of medicinal products is in a preceding section.

Regarding (e) peptide receptor-targeted radiation therapy, paediatric studies were recently started (e.g., Menda et al. 2010); no conclusion can be drawn at this time as relevant paediatric data are not yet available.

### ***Discussion of the concerned condition subject to the class waiver***

There are no paediatric data showing that above-mentioned classes of medicinal products (androgen receptor modulators, oestrogen receptor modulators, growth and sex hormones as well as their releasing or inhibiting factors, sex hormone-metabolism modulator medicinal products as well as first-

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<sup>8</sup> <http://www.esmo.org/Guidelines/Neuroendocrine-Tumours>

generation taxoid medicinal products) are safe and effective for treatment of gastroenteropancreatic neuroendocrine tumours and gastric carcinoids, and no such data will be available.

The existing paediatric data indicate that these classes of medicinal products are likely ineffective in the paediatric population with the studied malignancies. Requirements for paediatric studies should be waived for medicinal products of these classes in the concerned condition. This waiver should not apply when any of these classes of medicinal products are proposed for treatment of other diseases.

Unprecedented pharmacological properties in these classes of medicinal products, and unprecedented therapeutic situations in the disease, should lead to a specific evaluation of any recommendation to fulfil unmet needs or to ascertain significant therapeutic benefits in the paediatric population.

The existing paediatric data for immunomodulatory cytokine medicinal products are used as a basis of evidence for treatment of paediatric patients. Requirements for further paediatric studies should hence be waived for this class of medicinal products in the concerned condition. To require paediatric studies may not be justified by expected therapeutic benefit. This waiver should not apply when these classes of medicinal products are proposed for treatment of other diseases.

### **Ovarian carcinoma, Fallopian tube carcinoma, endometrial carcinoma, cervix and corpus uteri carcinoma, peritoneal carcinoma**

In order to be comprehensive, the review and consequences apply to the group of conditions of gynaecological epithelial malignant neoplasms, which includes diseases such as ovarian carcinoma, Fallopian tube carcinoma, endometrial carcinoma and cervix and corpus uteri carcinoma; peritoneal carcinoma is also included in this group of conditions as this is similarly treated and may be related to such the other carcinomas mentioned. Non-epithelial ovarian cancers such as germ cell tumours are not included in this group of conditions. For the medical treatment of such diseases, (a) chemotherapy and (b) targeted anti-cancer medicines are mentioned in recent guidelines.<sup>9</sup> For these types of medical treatments, medicines from one or more classes of medicinal products are authorised in Europe for the treatment of gynaecological epithelial malignant neoplasms, including (a) paclitaxel, trabectedin, doxorubicin (pegylated liposomal), topotecan and (b) bevacizumab, olaparib.

#### ***Discussion of medicines used in adults with a gynaecological epithelial malignant neoplasm, as investigated in paediatric conditions***

Regarding (a) chemotherapy, this includes the class of first-generation taxoid medicinal products, for which relevant paediatric data are reviewed above (section breast carcinoma). The medicinal product trabectedin belongs to the class of ecteinascidins, not otherwise specified plant alkaloids and natural products, in which it is currently the only authorised medicinal product. A paediatric study with trabectedin (Baruchel et al. 2012) has been assessed by the CHMP. The study included 50 paediatric patients with a rhabdomyosarcoma, Ewing sarcoma or non-rhabdomyosarcoma soft tissue sarcoma, and among 40 patients in whom response could be evaluated, an objective (partial) response was observed in a single patient. Subsequently the CHMP concluded that trabectedin should not be used to treat children with a paediatric sarcoma because of efficacy concerns (European Medicines Agency 2014). Other classes of medicinal products used for chemotherapy are topoisomerase inhibitors (topotecan) and anthracyclines (pegylated liposomal doxorubicin), which are being used and further studied for treatment of paediatric patients; therefore, conclusions cannot be drawn at this time for these classes of medicinal products.

Regarding (b) *targeted anti-cancer medicines*, these encompass several classes of medicinal products with which paediatric studies are ongoing, and no conclusions can be drawn at this time.

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<sup>9</sup> <http://www.esmo.org/Guidelines/Gynaecological-Cancers>

### ***Discussion of the concerned condition subject to the class waiver***

There are no paediatric data showing that first-generation taxoid medicinal products and ecteinascidins medicinal products are safe and effective for treatment of gynaecological epithelial malignant neoplasms, and no such data will be available. The existing paediatric data indicate that these classes of medicinal products are likely ineffective in the paediatric population with the studied malignancies. Requirements for paediatric studies should be waived for medicinal products of these classes in the concerned condition. These waivers should not apply when any of these classes of medicinal products are proposed for treatment of other diseases. Unprecedented pharmacological properties in these classes of medicinal products, and unprecedented therapeutic situations in the disease, should lead to a specific evaluation of any recommendation to fulfil unmet needs or to ascertain significant therapeutic benefits in the paediatric population.

### **Gastric adenocarcinoma, adenocarcinoma of the colon and rectum**

The group of conditions that includes diseases such as gastric adenocarcinoma and adenocarcinoma of the colon and rectum was defined as intestinal malignant neoplasms. For the medical treatment of these diseases, (a) chemotherapy and (b) targeted anti-cancer medicines are mentioned in recent guidelines.<sup>10</sup> For these types of medical treatments, medicines from one or more classes of medicinal products are authorised in Europe for the treatment of intestinal malignant neoplasms,<sup>11</sup> including (a) capecitabine, docetaxel, epirubicin, 5-fluorouracil, irinotecan, oxaliplatin, tegafur / gimeracil / oteracil, raltitrexed and (b) aflibercept, bevacizumab, cetuximab, panitumumab, ramucirumab, regorafenib, trastuzumab.

### ***Discussion of medicines used in adults with an intestinal malignant neoplasm, as investigated in paediatric conditions***

Regarding (a) chemotherapy medicinal products for treatment of intestinal malignant neoplasms, the authorised medicines belong to several different classes of mechanisms of medicinal products. Capecitabine, 5-fluorouracil and tegafur / gimeracil / oteracil belong to the class of pyrimidine- and pyrimidine analogue-containing medicinal products. The relevant paediatric data for this class as well as for the classes of first-generation taxoid medicinal products and first- and second generation platinum-containing medicinal products have been reviewed in preceding sections and the conclusions for the paediatric population remain as per above. Raltitrexed belongs to the class of thymidylate synthase inhibitor medicinal products; it is authorised but seems not to be mentioned in guidelines and therefore the paediatric data are discussed in a subsequent section (lung malignant neoplasms); the conclusions based on the paediatric data for this class of medicinal products remain as per the discussion below. Other classes of medicinal products used for chemotherapy of intestinal malignant neoplasms are topoisomerase inhibitors (irinotecan) and anthracyclines (epirubicin), which are being studied for treatment of paediatric patients and, therefore, no conclusions can be drawn at this time.

Regarding (b) targeted anti-cancer medicines for treatment of intestinal malignant neoplasms, the authorised medicines belong to several different classes of medicinal products: Trastuzumab belongs to the class of Her- / Epidermal growth factor-receptor antibody medicinal products, for which relevant paediatric data have been reviewed above (section breast carcinoma) and the conclusions remain the same as above. However, paediatric studies with bevacizumab and regorafenib are ongoing and paediatric investigation plans have been agreed for these medicinal products; for their class of targeted medicinal products, therefore conclusions cannot be drawn at this time.

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<sup>10</sup> <http://www.esmo.org/Guidelines/Gastrointestinal-Cancers>

<sup>11</sup> Centrally authorised medicinal products:  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar\\_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=prostate&keywordSearch=Submit&searchType=ti&taxonomyPath=&treeNumber=&searchGenericType=generics](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=prostate&keywordSearch=Submit&searchType=ti&taxonomyPath=&treeNumber=&searchGenericType=generics)

### ***Discussion of the concerned condition subject to the class waiver***

There are no paediatric data showing that above-mentioned classes of medicinal products (first-generation taxoid medicinal products, thymidylate synthase inhibitor medicinal products and Her- / Epidermal growth factor-receptor antibody medicinal products) are safe and effective for treatment of intestinal malignant neoplasms, and no such data will be available. The existing paediatric data indicate that these classes of medicinal products are likely ineffective in the paediatric population with the studied malignancies. Requirements for paediatric studies should be waived for medicinal products of these classes in the concerned condition. This waiver should not apply when any of these classes of medicinal products are proposed for treatment of other diseases. Unprecedented pharmacological properties in these classes of medicinal products, and unprecedented therapeutic situations in the disease, should lead to a specific evaluation of any recommendation to fulfil unmet needs or to ascertain significant therapeutic benefits in the paediatric population.

The existing paediatric data for pyrimidine- and pyrimidine analogue-containing medicinal products and first- and second generation platinum-containing medicinal products are used as a basis of evidence for treatment of paediatric patients. Requirements for further paediatric studies should hence be waived for this class of medicinal products in the concerned condition. To require paediatric studies may not be justified by expected therapeutic benefit. This waiver should not apply when these classes of medicinal products are proposed for treatment of other diseases.

### **Oropharyngeal, laryngeal or nasal epithelial carcinoma**

The group of conditions that includes diseases such as oropharyngeal, laryngeal or nasal epithelial carcinoma was defined as head and neck epithelial malignant neoplasms. For the medical treatment of such diseases, chemotherapy is mentioned in recent guidelines (referring to cisplatin, 5-fluorouracil, paclitaxel, docetaxel, gemcitabine, capecitabine, irinotecan, vinorelbine, ifosfamide, doxorubicin and oxaliplatin).<sup>12</sup> For this type of medical treatment, medicines from different classes of medicinal products are authorised in Europe for the treatment of head and neck epithelial malignant neoplasms,<sup>13</sup> including (a) chemotherapy medicinal products (docetaxel, fluorouracil, oxaliplatin), (b) the class of Her- / epidermal growth factor-receptor antibody medicinal products (cetuximab) and (c) temoporfin.

### ***Discussion of medicines used in adults with a head and neck epithelial malignant neoplasm, as investigated in paediatric conditions***

Regarding (a) chemotherapy medicinal products for treatment of head and neck epithelial malignant neoplasms, the authorised medicines include first-generation taxoids, pyrimidine- and pyrimidine analogue-containing medicinal products and first- and second-generation platinum-containing medicinal products. The recent paediatric data these classes have been reviewed in preceding sections and the conclusions for the paediatric population remain as per above.

For (b) Her- / epidermal growth factor-receptor antibody medicinal products, the paediatric data have been reviewed in a preceding section and the conclusion for the paediatric population remains as per above.

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<sup>12</sup> <http://www.esmo.org/Guidelines/Head-and-Neck-Cancers>

<sup>13</sup> Centrally authorised medicinal products:

[http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar\\_search.jsp&mid=WC0b01ac058001d124&searchTab=&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=neck&searchType=ti&taxonomyPath=Diseases.Cancer.Neoplasms+by+Site&treeNumber=&currentCategory=Head+and+Neck+Neoplasms&searchGenericType=generics](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=neck&searchType=ti&taxonomyPath=Diseases.Cancer.Neoplasms+by+Site&treeNumber=&currentCategory=Head+and+Neck+Neoplasms&searchGenericType=generics)

Temoporfin (c) is described as a photodynamic treatment and belongs to the class of photosensitising medicinal products. According to a review of anti-cancer medicines (Vassal 2009), temoporfin has “no rationale for other diseases in children” (that is, other than the cancer for which it is authorised in adults). A range of malignant diseases may present in the paediatric population with symptoms that can include the skin (from acute leukaemias, lymphomas, soft tissue tumours to neuroblastoma) or may present primarily in the skin (such as melanoma, certain subtypes lymphomas and a subtype of sarcoma). However, based on the Committee's expertise and after screening relevant textbooks (Pizzo & Poplack 2011), local anti-cancer photodynamic treatments are generally not part of the anti-cancer treatment regimens given as paediatric medical care. The exception is basal cell carcinoma, a type of primary skin malignant neoplasm, which is known complication of the inborn Gorlin-Goltz syndrome and which may occur at the age of puberty. Recent expert recommendations for this rare disease that affects the paediatric and adult populations include photodynamic therapy of basal cell carcinomas (Basset-Seguín et al. 2014). There seems some experience in children affected by this disease. There are also literature publications on photodynamic therapy of angiofibromas such as occurring in the inborn tuberous sclerosis syndrome or of haemangioblastoma in the eye, in children. Taken together, some studies of photodynamic treatments in children are available and their limited number seems understandable.

### ***Discussion of the concerned condition subject to the class waiver***

There are no paediatric data showing that above-mentioned classes of medicinal products (first-generation taxoids, pyrimidine- and pyrimidine analogue-containing medicinal products, first- and second generation platinum-containing medicinal products, Her- / epidermal growth factor-receptor antibody medicinal products and photosensitising medicinal products) are safe and effective for treatment of head and neck epithelial malignant neoplasms, and no such data will be available.

The existing paediatric data indicate that first-generation taxoid medicinal products and Her- / epidermal growth factor-receptor antibody medicinal products are likely ineffective in the paediatric population with the studied malignancies. Requirements for paediatric studies should be waived for medicinal products of these classes in the concerned condition. This waiver should not apply when any of these classes of medicinal products are proposed for treatment of other diseases. Unprecedented pharmacological properties in these classes of medicinal products, and unprecedented therapeutic situations in the disease, should lead to a specific evaluation of any recommendation to fulfil unmet needs or to ascertain significant therapeutic benefits in the paediatric population.

The existing paediatric data for pyrimidine- and pyrimidine analogue-containing medicinal products, first- and second generation platinum-containing medicinal products and photosensitising medicinal products form the basis of evidence for treatment of paediatric patients. Requirements for further paediatric studies should hence be waived for this class of medicinal products in the concerned condition. To require paediatric studies may not be justified by expected therapeutic benefit. This waiver should not apply when these classes of medicinal products are proposed for treatment of other diseases.

### **Small and non-small cell lung carcinoma, mesothelioma**

In order to be comprehensive, the review and consequences apply to the group of conditions of lung malignant neoplasms, which includes diseases such small cell lung carcinoma and non-small cell lung carcinoma as well as mesothelioma, as these manifest in the same anatomical region. For the medical treatment of such diseases, (a) chemotherapy and (b) targeted anti-cancer medicines are mentioned in recent guidelines.<sup>14</sup> For these types of medical treatments, medicines from several classes of

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<sup>14</sup> <http://www.esmo.org/Guidelines/Lung-Cancer>

medicinal products are authorised in Europe for the treatment of lung malignant neoplasms,<sup>15</sup> including (a) cisplatin, cyclophosphamide, docetaxel, doxorubicin, etoposide, gemcitabine, paclitaxel, pemetrexed, topotecan, vinorelbine and (b) afatinib, bevacizumab, crizotinib, erlotinib, gefinitib, nintedanib.

### ***Discussion of medicines used in adults with a lung malignant neoplasm, as investigated in paediatric conditions***

Regarding (a) chemotherapy, this includes the class of first-generation taxoid medicinal products (docetaxel), the first- and second generation platinum-containing medicinal products (cisplatin) and pyrimidine and pyrimidine analogue-containing medicinal products (gemcitabine). The relevant paediatric data for these classes of medicinal products been reviewed in preceding sections and the conclusions for the paediatric population remain as per above. Pemetrexed and raltitrexed (authorised for treatment of intestinal malignant neoplasm, above) belong to the class of thymidylate synthase inhibitor medicinal products. Paediatric studies have been reported with single-agent pemetrexed, including an early (phase 1) study involving 33 children (Malempati et al. 2007) and, recently, the subsequent therapeutic-exploratory (phase 2) study involving 72 children with a refractory solid malignant tumour (Warwick et al. 2013). In none of the 68 evaluable patients in the therapeutic-exploratory study, an objective response such as a partial or a complete tumour response (shrinkage) occurred. Amongst other patients, both pemetrexed studies included in total 38 patients with a tumour of the central nervous system (CNS), for which a rationale to study this medicinal product was based on previous findings of certain tumour types highly expressing folate receptors. A study with single-agent raltitrexed in 21 children with refractory leukaemia had been reported earlier one complete and two partial haematological responses (Horton et al. 2005); no further paediatric studies seemed to have been undertaken and the reported proportion of responses is considered low. In conclusion, representative medicinal products from the class of thymidylate synthase inhibitor medicinal products have been shown to lack relevant anti-cancer activity in the studied paediatric diseases.

Other classes of medicinal products used for chemotherapy are topoisomerase inhibitors (topotecan), alkylating agents (cyclophosphamide), vinca alkaloids (vinorelbine), epipodophyllotoxins (etoposide) and anthracyclines (doxorubicin), which are being used and further studied for treatment of paediatric patients and therefore a waiver cannot be considered for these classes of medicinal products for treatment of lung malignant neoplasms.

Regarding (b) targeted anti-cancer cancer medicines, the medicinal products authorised for treatment of lung malignant neoplasms are from the classes of anti-angiogenic medicinal products, of primarily ALK inhibiting medicinal products and primarily EGFR inhibiting medicinal products. At this time, paediatric studies with medicinal products from each of these classes are ongoing (e.g. bevacizumab, crizotinib, erlotinib) and a paediatric investigation plan has been agreed for bevacizumab. Therefore, no conclusions can be drawn concerning these classes of medicinal products for the time being.

### ***Discussion of the concerned condition subject to the class waiver***

There are no paediatric data showing that above-mentioned classes of medicinal products (first-generation taxoid medicinal products, pyrimidine and pyrimidine analogue-containing medicinal products, thymidylate synthase inhibitor medicinal products and first- and second generation platinum-containing medicinal products) are safe and effective for treatment of lung malignant neoplasms, and no such data will be available.

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<sup>15</sup> Centrally authorised medicinal products:

[http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar\\_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=prostate&keywordSearch=Submit&searchType=ti&taxonomyPath=&treeNumber=&searchGenericType=generics](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=prostate&keywordSearch=Submit&searchType=ti&taxonomyPath=&treeNumber=&searchGenericType=generics)



The existing paediatric data indicate that these classes of first-generation taxoid medicinal products and thymidylate synthase inhibitor medicinal products are likely ineffective in the paediatric population with the studied malignancies. Requirements for paediatric studies should be waived for medicinal products of these classes in the concerned condition. This waiver should not apply when any of these classes of medicinal products are proposed for treatment of other diseases. Unprecedented pharmacological properties in these classes of medicinal products, and unprecedented therapeutic situations in the disease, should lead to a specific evaluation of any recommendation to fulfil unmet needs or to ascertain significant therapeutic benefits in the paediatric population.

The existing paediatric data for the classes of pyrimidine and pyrimidine analogue-containing medicinal products and first- and second generation platinum-containing medicinal products form the basis of evidence for treatment of paediatric patients. Requirements for further paediatric studies should hence be waived for this class of medicinal products in the concerned condition. To require paediatric studies may not be justified by expected therapeutic benefit. This waiver should not apply when these classes of medicinal products are proposed for treatment of other diseases.

## **Primary gout**

The treatment of primary gout involves treatment of acute attacks and secondary prevention of flares with treatments that deplete urate stores. Medicinal products for treatment of primary gout (excluding symptomatic treatment) include for example colchicine, febuxostat, pegloticase.

### ***Discussion of medicines used in adults with primary gout, as investigated in paediatric conditions***

Colchicine belongs to the class of colchicum alkaloids (colchicine and its derivatives) medicinal products, for which paediatric studies have been assessed (Medicines & Healthcare products Regulatory Agency (MHRA) 2012). Accordingly, a new indication colchicine was recommended: prevention of attacks and of amyloidosis in children with familial Mediterranean fever, an auto-inflammatory syndrome. Such a use had previously been suggested for paediatric medical care based on studies in children (Kallinich et al. 2007). Taken together, it is understood that colchicine is an established part of the treatment administered as part of the medical care of children with familial Mediterranean fever. For febuxostat and pegloticase, paediatric studies are ongoing and paediatric investigation plans have been agreed. Therefore, no conclusions can be drawn at this time for these medicinal products.

### ***Discussion of the concerned condition subject to the class waiver***

There are no paediatric data showing that colchicum alkaloids (colchicine and its derivatives) medicinal products are safe and effective for treatment of primary gout, and no such data will be available. The existing paediatric data for colchicum alkaloids (colchicine and its derivatives) medicinal products form the basis of evidence for treatment of paediatric patients. Requirements for further paediatric studies should hence be waived for this class of medicinal products in the concerned condition. To require paediatric studies may not be justified by expected therapeutic benefit. This waiver should not apply when these classes of medicinal products are proposed for treatment of other diseases.

## **Benign prostatic hyperplasia**

For medical treatment of benign prostatic hyperplasia (or hypertrophy), several different classes of medicinal products are being used. Authorised medicinal products for treatment of benign prostatic hyperplasia include alfuzosin, doxazosin, finasteride, induramin, silodosin, tadalafil, tamsulosin. These belong to the classes of specifically androgen antagonists (e.g., finasteride), the class of alpha-

adrenergic receptor blocking medicinal products (e.g., tamsulosin) and the class of phosphodiesterase type 5 inhibitors (e.g., tadalafil).

### ***Discussion of medicines used in adults with benign prostatic hyperplasia, as investigated in paediatric conditions***

Paediatric studies were conducted for example in hyperandrogenism and, with flutamide, in congenital adrenal hyperplasia; the latter studies are discussed even though no general recommendations for paediatric medical care are given (Speiser et al. 2010). Paediatric studies with tamsulosin in children with a lower urinary tract syndrome or dysfunctional voiding have recently been assessed (Medicines & Healthcare products Regulatory Agency (MHRA) 2012). The paediatric evidence was considered inconclusive and therefore, no conclusions can be drawn here for the class of alpha-adrenergic receptor blocking medicinal products at this time. For tadalafil, paediatric studies are ongoing and a paediatric investigation plan has been agreed; no conclusions can therefore be drawn for the class of phosphodiesterase 5 inhibitors.

### ***Discussion of the concerned condition subject to the class waiver***

There are no paediatric data showing that androgen antagonists are safe and effective for treatment of benign prostatic hyperplasia, and no such data will be available. The existing paediatric data for androgen antagonist medicinal products may provide some evidence for treatment of paediatric patients in medical care. Requirements for further paediatric studies should hence be waived for this class of medicinal products in the concerned condition. To require paediatric studies may not be justified by expected therapeutic benefit. This waiver should not apply when these classes of medicinal products are proposed for treatment of other diseases.

## **Melanoma, basal cell carcinoma, actinic keratosis**

In order to be inclusive, the review and consequences apply to skin malignant neoplasms, which include melanoma, basal carcinoma and squamous cell carcinoma of the skin; the review also includes actinic keratosis, which can evolve into squamous cell carcinoma. For the medical treatment of these diseases, (a) chemotherapy (dacarbazine, temozolomide, paclitaxel, fotemustine, carboplatin or others), (b) targeted anti-cancer medicines (anti-PD1 antibodies, BRAF inhibitors, c-kit inhibitors, MAPK/ERK kinase inhibitors), (c) immunomodulatory cytokines (interleukin-2 [aldesleukin], interferon), (d) photodynamic treatment (5-aminolevulinic acid / methyl aminolevulinate), (e) local treatments (fluorouracil) are used inside and outside of trials and are mentioned in a recent guideline<sup>16</sup> as well as in a systematic review (Lansbury et al. 2013). Medicines from one or more classes of medicinal products are authorised in Europe for the treatment of skin malignant neoplasms,<sup>17</sup> including (a) bleomycin, dacarbazine, (b) dabrafenib, ipilimumab, trametinib, vemurafenib, (c) interferon alfa-2b, (d) 5-aminolevulinic acid and (e) imiquimod, ingenol, 5-fluorouracil.

### ***Discussion of medicines used in adults with a skin malignant neoplasm, as investigated in paediatric conditions***

Regarding (a) chemotherapy, bleomycin is a unique, non-anthracycline medicine in the class of anti-cancer antibiotics. More than 90 reports of paediatric studies that were completed before 2007 have been listed by pharmaceutical companies for submissions under Article 45 of the paediatric regulation

<sup>16</sup> <http://www.esmo.org/Guidelines/Melanoma/Cutaneous-Melanoma>

<sup>17</sup> Centrally authorised medicinal products:  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar\\_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=prostate&keywordSearch=Submit&searchType=ti&taxonomyPath=&treeNumber=&searchGenericTypes=generics](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=prostate&keywordSearch=Submit&searchType=ti&taxonomyPath=&treeNumber=&searchGenericTypes=generics)

(publicly available in the corresponding database of the agency).<sup>18</sup> At this time, the assessment of the results of these paediatric studies has not been completed. Therefore, no conclusions can be drawn at this time for this class of anti-cancer antibiotic medicinal product. Dacarbazine is a chemotherapy medicinal product which, among all alkylating agents, belongs together with temozolomide to the class of alkylating-methylating medicinal products (Pizzo & Poplack 2011, p 304). In paediatric medical care, dacarbazine is used as part of some treatment protocols for patients with Hodgkin disease (Pizzo & Poplack 2011, overview p 649). Furthermore, temozolomide is used for treatment of paediatric patients with brain tumours, neuroblastoma, Hodgkin lymphoma and sarcomas (Pizzo & Poplack 2011, p 290), and temozolomide is authorised for treatment of children with a recurring or growing glioblastoma brain tumour.

Regarding (b) targeted anti-cancer medicines, paediatric studies for example with dabrafenib, dasatinib, ipilimumab, pembrolizumab and trametinib are ongoing, and paediatric investigation plans have been agreed; at this time, therefore, conclusions cannot be drawn.

Regarding (c) immunomodulatory cytokines, this includes a range of active substances. For example, interferons are used in the treatment of paediatric patients with diseases such as infections (hepatitis B, hepatitis C, HPV); myocarditis; uveitis; multiple sclerosis and Guillain-Barré syndrome; Castleman disease; congenital dyserythropoietic anaemia; large haemangiomas; asthma; psoriasis. Furthermore, paediatric studies are ongoing in some of these diseases, and paediatric investigation plans have been agreed for certain interleukin and interferon medicinal products. A randomised controlled trial has recently completed recruitment of children and young adult patients with an osteosarcoma (Whelan et al. 2015). The trial has the purpose to investigate how well two different chemotherapy regimens, one with and the other without interferon alfa-2b, work to treat this disease. It was discussed that this large trial can be expected to clarify the value of interferon in the treatment of osteosarcoma. A report of a non-controlled study of 45 children and young adults with a nasopharyngeal carcinoma, a rare paediatric malignant neoplasm, found that a multimodal therapy including interferon beta resulted in complete remission in almost all patients by the end of therapy and in an event-free survival rate of 92% after a median observation time of 30 months (Buehrlen et al. 2012). It is understood that interferon beta is administered as part of the medical care in Europe of children with nasopharyngeal carcinoma. Paediatric studies that include the use of interleukin 2 (aldesleukin) have been reported mostly in patients with neuroblastoma, in whom it is thought to enhance the anti-cancer activity for example of dinutuximab; dinutuximab has recently been recommended for granting of a marketing authorisation in Europe concerning this combination use for treatment of certain paediatric patients with a neuroblastoma.

Regarding (d) photodynamic treatments, these correspond to the class of photosensitising medicinal products, for which paediatric data have been reviewed in a preceding section (head and neck epithelial malignant neoplasms) and the conclusions for the paediatric population remain as per above.

Regarding (e) local treatments, these are from different classes, such as pyrimidine- and pyrimidine analogue-containing medicinal products, for which paediatric data have been reviewed in a preceding section (breast malignant neoplasms) and the conclusions for the paediatric population remain as per above.

### ***Discussion of the concerned condition subject to the class waiver***

There are no paediatric data showing that above-mentioned classes of medicinal products (pyrimidine- and pyrimidine analogue-containing medicinal products, alkylating-methylating medicinal products and

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<sup>18</sup> [http://art45-paediatric-studies.ema.europa.eu/clinicaltrials/search\\_results.php?Category=&Active\\_substance\\_INN=bleomycin&cTitle=&Therapeutic\\_area\\_MESH\\_terms=&Scope\\_of\\_the\\_study=&ATC\\_Code=&cBrands=&Clinical+Trials\\_submit=Submit](http://art45-paediatric-studies.ema.europa.eu/clinicaltrials/search_results.php?Category=&Active_substance_INN=bleomycin&cTitle=&Therapeutic_area_MESH_terms=&Scope_of_the_study=&ATC_Code=&cBrands=&Clinical+Trials_submit=Submit)

immunomodulatory cytokine medicinal products) are safe and effective for treatment of skin malignant neoplasms, and no such data will be available.

The existing paediatric data for pyrimidine- and pyrimidine analogue-containing medicinal products, alkylating-methylating medicinal products and immunomodulatory cytokine medicinal products form the basis of evidence for treatment of paediatric patients. Requirements for further paediatric studies should hence be waived for this class of medicinal products in the concerned condition. To require paediatric studies may not be justified by expected therapeutic benefit. This waiver should not apply when these classes of medicinal products are proposed for treatment of other diseases.

## **Pancreatic malignant neoplasms**

The group of conditions that includes diseases such as pancreatic adenocarcinoma was defined as pancreatic malignant neoplasms. For the medical treatment of these diseases, (a) chemotherapy (irinotecan and oxaliplatin) and (b) a targeted anti-cancer therapy (erlotinib) are mentioned in a recent guideline.<sup>19</sup> For these two types of medical treatments, medicines from one or more classes of medicinal products are authorised in Europe for the treatment of pancreatic malignant neoplasm,<sup>20</sup> including (a) fluorouracil, gemcitabine, paclitaxel and (b) erlotinib, everolimus.

### ***Discussion of medicines used in adults with a pancreatic malignant neoplasm, as investigated in paediatric conditions***

Regarding (a) chemotherapy, fluorouracil and gemcitabine belong to the class of pyrimidine- and pyrimidine analogue-containing medicinal products and paclitaxel to the class of first-generation taxoid medicinal products, for each of which relevant paediatric data have been reviewed in a preceding section (breast malignant neoplasms) and the conclusions for the paediatric population remain as per above.

Regarding (b) targeted anti-cancer medicines, the authorised medicinal products authorised for treatment of pancreatic malignant neoplasms are from the classes of primarily EGFR inhibiting medicinal products and primarily mTOR inhibiting medicinal products; paediatric studies with medicinal products from each of these classes are ongoing, and a paediatric investigation plan has been agreed for everolimus. Therefore, no conclusions can be drawn at this time for these classes of medicinal products.

### ***Discussion of the concerned condition subject to the class waiver***

There are no paediatric data showing that above-mentioned classes of medicinal products (first-generation taxoids, pyrimidine- and pyrimidine analogue-containing medicinal products) are safe and effective for treatment of head and neck epithelial malignant neoplasms, and no such data will be available.

The existing paediatric data indicate that first-generation taxoid medicinal product are likely ineffective in the paediatric population with the studied malignancies. Requirements for paediatric studies should be waived for medicinal products of these classes in the concerned condition. This waiver should not apply when any of these classes of medicinal products are proposed for treatment of other diseases. Unprecedented pharmacological properties in these classes of medicinal products, and unprecedented

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<sup>19</sup> <http://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Pancreatic-Adenocarcinoma>

<sup>20</sup> Centrally authorised medicinal products:

[http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar\\_search.jsp&mid=WC0b01ac058001d124&searchTab=&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=Enter+keywords&searchType=name&taxonomyPath=Diseases.Cancer.Neoplasms+by+Site.Digestive+System+Neoplasms&treeNumber=&currentCategory=Pancreatic+Neoplasms&searchGenericType=generics](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=Enter+keywords&searchType=name&taxonomyPath=Diseases.Cancer.Neoplasms+by+Site.Digestive+System+Neoplasms&treeNumber=&currentCategory=Pancreatic+Neoplasms&searchGenericType=generics)

therapeutic situations in the disease, should lead to a specific evaluation of any recommendation to fulfil unmet needs or to ascertain significant therapeutic benefits in the paediatric population.

The existing paediatric data for pyrimidine- and pyrimidine analogue-containing medicinal products form the basis of evidence for treatment of paediatric patients. Requirements for further paediatric studies should hence be waived for this class of medicinal products in the concerned condition. To require paediatric studies may not be justified by expected therapeutic benefit. This waiver should not apply when these classes of medicinal products are proposed for treatment of other diseases.

## **Myeloproliferative neoplasms**

In order to be inclusive, the review covered the group of myeloproliferative neoplasms, which include chronic myeloid leukaemia, chronic neutrophilic leukaemia, polycythaemia vera, primary myelofibrosis, essential thrombocythaemia, chronic eosinophilic leukaemia and mastocytosis, as identified as a major group (Swerdlow et al. 2008, p 18) characterised by maintained effective blood formation (haematopoiesis), increased blood cell counts, anomalous megakaryocytes and enlargement of for example the spleen or liver. For the medical treatment of myeloproliferative neoplasms, (a) chemotherapy, (b) targeted anti-cancer medicines, (c) immunomodulatory medicines and (d) supportive medicines are mentioned in recent guidelines<sup>21</sup> and in a review (Barosi et al. 2012). For these types of medical treatments, medicines from one or more classes of medicinal products are authorised in Europe for the treatment of myeloproliferative neoplasms, such as (a) busulfan, chlorambucil, cyclophosphamide, hydroxycarbamide (hydroxyurea), vincristine, (b) bosutinib, dasatinib, imatinib, nilotinib, ponatinib, ruxolitinib, (c) interferon alfa-2b, thalidomide, lenalidomide, pomalidomide and (d) anagrelide.

### ***Discussion of medicines used in adults with a myeloproliferative neoplasm, as investigated in paediatric conditions***

Regarding (a) chemotherapy, this encompasses several classes of medicinal products. Hydroxycarbamide (hydroxyurea) belongs to the class of ribonucleotide reductase beta-2 inhibitor medicinal products and is used for the treatment of several of the subtypes of myeloproliferative neoplasms. In a paediatric study, hydroxycarbamide was randomised as add-on to standard of care in 48 children with hyperleukocytosis in acute lymphoblastic leukaemia (Sharma et al. 2014, sec.O-079). According to the preliminary report, the total leukocyte count was much more often reduced in the hydroxyurea group, whereas no differences in complications (e.g., tumour lysis syndrome and death) were found. The authors conclude to recommend hydroxycarbamide (hydroxyurea) in this setting of hyperleukocytosis. In analogy to acute lymphoblastic leukaemia, hydroxycarbamide (hydroxyurea) is mentioned for reducing circulating blasts counts in chronic myeloid leukaemia in children (Pizzo & Poplack 2011, p 621). Other classes of medicinal products used for chemotherapy are classical, primarily alkylating agents (that is, more complex than methylating agents) are busulfan, cyclophosphamide and chlorambucil, which are authorised in Europe for use in the paediatric population, including for treatment of various lymphoma subtypes. Primarily alkylating agents are an established as part of the treatment administered for the medical care of children with a malignant neoplasm (Pizzo & Poplack 2011, pp 290 and 299). Recent paediatric studies have also contributed to refine paediatric medical care posology recommendations (for example, Michel et al. 2011). Other classes of medicinal products used for chemotherapy are vinca alkaloids (vincristine), which are being used and further studied for treatment of paediatric patients; therefore, no further conclusions were drawn at this time.

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<sup>21</sup> <http://www.esmo.org/Guidelines/Haematological-Malignancies/Chronic-Myeloid-Leukemia>,  
<http://www.cancer.gov/cancertopics/pdq/treatment/myeloproliferative/HealthProfessional>

Regarding (b) targeted anti-cancer medicines, these encompass several classes of medicinal products with which paediatric studies are ongoing, including medicinal products for which paediatric investigation plans have been agreed; therefore, no conclusions can be drawn at this time.

Regarding (c) immunomodulatory medicines, these represent different classes of medicinal products including immunomodulatory cytokine medicinal products, for which paediatric data have been reviewed in a preceding section (skin malignant neoplasms) and the conclusions for the paediatric population remain as per above. For the thalidomide-analogues pomalidomide and lenalidomide, product-specific waivers have previously been discussed; also, a paediatric study with lenalidomide (Berg et al. 2011) was noted, but no conclusive data are available. Therefore, no further conclusions concerning thalidomide and analogues can be drawn at this time.

Regarding (d) supportive medicines, paediatric studies with anagrelide are ongoing and a paediatric investigation plan has been agreed; therefore, no conclusions can be drawn at this time.

### ***Discussion of the concerned condition subject to the class waiver***

There are no paediatric data showing that above-mentioned classes of medicinal products (ribonucleotide reductase beta-2 inhibitor medicinal products, primarily alkylating medicinal products, immunomodulatory cytokine medicinal products) are safe and effective for treatment of head and neck epithelial malignant neoplasms, and no such data will be available.

The existing paediatric data for ribonucleotide reductase beta-2 inhibitor medicinal products, primarily alkylating medicinal products and immunomodulatory cytokine medicinal products form the basis of evidence for treatment of paediatric patients. Requirements for further paediatric studies should hence be waived for this class of medicinal products in the concerned condition. To require paediatric studies may not be justified by expected therapeutic benefit. This waiver should not apply when these classes of medicinal products are proposed for treatment of other diseases.

## **Mature B, T and NK cell neoplasms**

In order to be inclusive, the review covers the group of conditions of mature B, T and NK cell neoplasms, which include non-Hodgkin lymphomas such as chronic lymphocytic leukaemia / small lymphocytic lymphoma, hairy cell leukaemia, lymphoplasmacytic lymphoma, plasma cell myeloma, MALT lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, Burkitt lymphoma, mycosis fungoides, cutaneous T-cell lymphoma, peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated). The mature B cell neoplasms and T or NK cell neoplasms are major subgroups of lymphoid neoplasms (Swerdlow et al. 2008, p 158), and the included diseases are respectively characterised by a specific stage of differentiation arrest of lymphatic cells (B, T or NK) that gives rise to a clonal lymphoid tumour. For the medical treatment of these diseases, (a) chemotherapy, (b) targeted anti-cancer medicines and (c) immunomodulatory medicines are mentioned in recent guidelines.<sup>22</sup> For these types of medical treatments, medicines from one or more classes of medicinal products are authorised in Europe for the treatment of mature B, T and NK cell neoplasms, including (a) bendamustine, bleomycin, cladribine, cyclophosphamide, doxorubicin, fludarabine, pixantrone, pralatrexate, (b) brentuximab vedotin, bexarotene, bortezomib, <sup>90</sup>Yttrium labelled ibritumomab tiuxetan, ibrutinib, idelalisib, rituximab, romidepsin, temsirolimus, (c) denileukin diftitox, interferon alfa-2b, lenalidomide, pomalidomide, thalidomide.

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<sup>22</sup> <http://www.esmo.org/Guidelines/Haematological-Malignancies>

***Discussion of medicines used in adults with a mature B, T or NK cell neoplasm, as investigated in paediatric conditions***

Regarding (a) chemotherapy for treatment of mature B, T and NK cell neoplasms, the authorised medicines belong to several different classes of medicinal products. Paediatric studies with pixantrone and pralatrexate are ongoing and paediatric investigation plans have been agreed for these medicinal products; furthermore, while some doxorubicin-containing medicinal products are authorised for certain paediatric uses, studies were found to be ongoing and to investigate paediatric questions. Therefore, conclusions cannot be drawn for their class of topoisomerase II inhibiting medicinal products at this time. Paediatric data on medicines belonging to the class of primarily alkylating medicinal products have been discussed in the preceding section (myeloproliferative neoplasms) and the conclusions for the paediatric population remain as per above.

Regarding (b) targeted anti-cancer medicines, for treatment of mature B, T and NK cell neoplasms, the authorised medicines belong to several different classes of medicinal products. Paediatric studies with brentuximab vedotin, idelalisib and rituximab are ongoing and paediatric investigation plans have been agreed for these medicinal products; therefore, no conclusions can be drawn at this time for these medicinal products and their classes. Bexarotene belongs to the class of retinoic X receptor (RXR)-activating medicinal products (which are different from retinoids such as tretinoin that bind to the retinoic acid receptor, RAR). A series of 15 patients (including 3 children) with a subcutaneous panniculitis-like T-cell lymphoma or with a cutaneous gamma/delta T-cell lymphoma who had been treated with bexarotene in a single, larger institution has been reported (Mehta et al. 2012). In this rare-disease setting, an overall high response rate is reported; maintenance of remission is reported for the paediatric patients.

Regarding (c) immunomodulatory medicines, these include immunomodulatory cytokine medicinal products, for which paediatric data have been reviewed in a preceding section (skin malignant neoplasms) and the conclusions for the paediatric population remain as per above. Also, these include thalidomide and analogues, for which paediatric information and data have been reviewed in the preceding section (mature B, T and NK cell neoplasms), where no further conclusions could be drawn.

***Discussion of the concerned condition subject to the class waiver***

There are no paediatric data showing that primarily alkylating medicinal products, retinoid X receptor-agonist medicinal products and immunomodulatory cytokine medicinal products are safe and effective for treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma, hairy cell leukaemia, multiple myeloma / plasma cell myeloma, follicular lymphoma, and no such data will be available.

The existing paediatric data for primarily alkylating medicinal products, retinoid X receptor-agonist medicinal products and immunomodulatory cytokine medicinal products form the basis of evidence for treatment of paediatric patients. Requirements for further paediatric studies should hence be waived for this class of medicinal products in the concerned condition. To require paediatric studies may not be justified by expected therapeutic benefit. This waiver should not apply when these classes of medicinal products are proposed for treatment of other diseases.

## 4. Overview

### ***Medicinal products that are likely to be ineffective in the paediatric population***

<b>Class of medicinal product</b>	<b>References</b>	<b>Group of conditions where the medicinal product is authorised for treatment</b>
Androgen receptor modulator, oestrogen receptor modulator, growth and sex hormone as well as their releasing or inhibiting factors, sex hormone-metabolism modulator medicinal products <sup>23</sup>	(Bourdeaut et al. 2009) (Janem et al. 2010) (Skapek et al. 2013) (Michalski et al. 2010)	<ul style="list-style-type: none"> <li>• Breast malignant neoplasms</li> <li>• Prostate malignant neoplasms</li> <li>• Neuroendocrine malignant neoplasms</li> </ul>
First-generation taxoid medicinal products <sup>24</sup>	(Horton et al. 2008) (Norwegian Medicines Agency 2010) (Sanofi 2012) (Jacobs et al. 2010)	<ul style="list-style-type: none"> <li>• Breast malignant neoplasms</li> <li>• Gynaecological epithelial malignant neoplasms</li> <li>• Prostate malignant neoplasms</li> <li>• Intestinal malignant neoplasms</li> <li>• Head and neck epithelial malignant neoplasms</li> <li>• Lung malignant neoplasms</li> <li>• Pancreatic malignant neoplasms</li> </ul>
Her-/Epidermal growth factor-receptor antibody medicinal products <sup>25</sup>	(Trippett et al. 2009) (Ebb et al. 2012) (European Medicines Agency 2009)	<ul style="list-style-type: none"> <li>• Breast malignant neoplasms</li> <li>• Intestinal malignant neoplasms</li> <li>• Head and neck epithelial malignant neoplasms</li> </ul>
Ecteinascidin medicinal products	(Baruchel et al. 2012) (European Medicines Agency 2014)	<ul style="list-style-type: none"> <li>• Gynaecological epithelial malignant neoplasms</li> </ul>
Thymidylate synthase inhibitor medicinal product <sup>26</sup>	(Warwick et al. 2013) (Horton et al. 2005) (Malempati et al. 2007)	<ul style="list-style-type: none"> <li>• Intestinal malignant neoplasms</li> <li>• Lung malignant neoplasms</li> </ul>

<sup>23</sup> Examples: Tamoxifen, Toremifene, Fulvestrant, Degarelix, Enzalutamide, Abiraterone, Somatostatin, Octreotide

<sup>24</sup> Examples: Paclitaxel, Docetaxel, Ixabepilone

<sup>25</sup> Examples: Trastuzumab, Pertuzumab

<sup>26</sup> Examples: Pemetrexed, Raltitrexed



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

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 <sup>27</sup>	(Kilburn et al. 2013) (Hoffmann-La Roche 2014) (Trobaugh-Lotrario & Katzenstein 2012) (Buehrlen et al. 2012)	<ul style="list-style-type: none"> <li>• Breast malignant neoplasms</li> <li>• Intestinal malignant neoplasms</li> <li>• Head and neck epithelial malignant neoplasms</li> <li>• Lung malignant neoplasms</li> <li>• Pancreatic malignant neoplasms</li> <li>• Skin malignant neoplasms</li> <li>• Actinic keratosis</li> </ul>
First- and second-generation platinum-containing medicinal products <sup>28</sup>	(Pizzo & Poplack 2011, p.301)	<ul style="list-style-type: none"> <li>• Urinary tract malignant neoplasms</li> <li>• Intestinal malignant neoplasms</li> <li>• Head and neck epithelial malignant neoplasms</li> <li>• Lung malignant neoplasms</li> </ul>
Immunomodulatory cytokine medicinal products <sup>29</sup>	(Buehrlen et al. 2012)	<ul style="list-style-type: none"> <li>• Neuroendocrine malignant neoplasms</li> <li>• Skin malignant neoplasms</li> <li>• Myeloproliferative neoplasms</li> <li>• Mature B, T and NK cell neoplasms</li> <li>• Neuroblastoma</li> </ul>
Photosensitising medicinal products	(Basset-Seguin et al. 2014)	<ul style="list-style-type: none"> <li>• Head and neck epithelial malignant neoplasms</li> </ul>
Colchicum alkaloids (colchicine and its derivatives)	(Medicines & Healthcare products Regulatory Agency (MHRA) 2012) (Kallinich et al. 2007)	<ul style="list-style-type: none"> <li>• Primary gout</li> <li>• Auto-inflammatory syndromes</li> </ul>

<sup>27</sup> Examples: 5-Fluorouracil, Capecitabine

<sup>28</sup> Examples: Cisplatin, carboplatin, oxaliplatin

<sup>29</sup> Examples: Interleukin 2, Interferon alpha

<b>Class of medicinal product</b>	<b>Reference(s)</b>	<b>Group of conditions where the medicinal product is used for the treatment of</b>
Alkylating-methylating medicinal products <sup>30</sup>	(Pizzo & Poplack 2011, pp.304, 649, 290)	<ul style="list-style-type: none"> <li>• Skin malignant neoplasms</li> <li>• Brain tumours</li> <li>• Neuroblastoma</li> <li>• Sarcoma</li> <li>• Hodgkin lymphoma</li> </ul>
Androgen antagonists <sup>31</sup>	(Speiser et al. 2010)	<ul style="list-style-type: none"> <li>• Benign prostatic hyperplasia</li> <li>• Congenital adrenal hyperplasia</li> <li>• Hyperandrogenism</li> </ul>
Ribonucleotide reductase beta-2 inhibitor medicinal products <sup>32</sup>	(Sharma et al. 2014, sec.O–079) (Pizzo & Poplack 2011, p 621)	<ul style="list-style-type: none"> <li>• Myeloproliferative neoplasms</li> <li>• Leukaemia</li> </ul>
Primarily alkylating medicinal products	(Pizzo & Poplack 2011, pp 290 and 299) (Michel et al. 2011)	<ul style="list-style-type: none"> <li>• Myeloproliferative neoplasms</li> <li>• Mature B, T and NK cell neoplasms</li> <li>• Hodgkin lymphoma</li> </ul>
Retinoic X receptor-activating medicinal products <sup>33</sup>	(Mehta et al. 2012)	<ul style="list-style-type: none"> <li>• Mature B, T and NK cell neoplasms</li> </ul>

<sup>30</sup> Examples: Dacarbazine (DTIC), Temozolomide

<sup>31</sup> Example: Finasteride

<sup>32</sup> Example: Hydroxycarbamide (hydroxyurea)

<sup>33</sup> Examples: Bendamustine, Carmustine (BCNU); Temoporfin; Bexarotene

**Previously granted, revoked and revised waivers**

<b>Condition in previous class condition waiver</b>	<b>Groups of condition or condition referred to in revised class waiver</b>	<b>Class(es) of medicinal product referred to in revised class waiver</b>	<b>Scientific assessment conclusion</b>
Oropharyngeal, laryngeal or nasal epithelial carcinoma (excluding nasopharyngeal carcinoma or lymphoepithelioma)	Head and neck epithelial malignant neoplasms	First-generation taxoid medicinal products  Her- / epidermal growth factor-receptor antibody medicinal products  Pyrimidine- and pyrimidine analogue-containing medicinal products  Photosensitising medicinal products  First- and second generation platinum-containing medicinal products	Likely ineffective  Likely ineffective  Do not represent significant therapeutic benefits  Do not represent significant therapeutic benefits  Do not represent significant therapeutic benefits
Lung carcinoma (small cell and non-small cell carcinoma)	Lung malignant neoplasms	First-generation taxoid medicinal products  Thymidylate synthase inhibitor medicinal products  First- and second-generation platinum-containing medicinal products	Likely ineffective  Likely ineffective  Do not represent significant therapeutic benefits
Basal cell carcinoma	Skin malignant neoplasm	Pyrimidine- and pyrimidine analogue-containing medicines  Alkylating-methylating medicines	Do not represent significant therapeutic benefits  Do not represent significant therapeutic benefits

Condition in previous class condition waiver	Groups of condition or condition referred to in revised class waiver	Class(es) of medicinal product referred to in revised class waiver	Scientific assessment conclusion
		Immunomodulatory cytokine medicinal products	Do not represent significant therapeutic benefits
Breast carcinoma	Breast malignant neoplasms	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	Likely ineffective
		First-generation taxoid medicinal products	Likely ineffective
		Her- / epidermal growth factor-receptor antibody medicinal products	Likely ineffective
		Pyrimidine- and pyrimidine analogue-containing medicines	Do not represent significant therapeutic benefits
Ovarian carcinoma (excluding rhabdomyosarcoma and germ cell tumours)	Gynaecological epithelial malignant neoplasms	First-generation taxoid medicinal products	Likely ineffective
		Ecteinascidin medicinal products	Likely ineffective
Fallopian tube carcinoma (excluding rhabdomyosarcoma and germ cell tumours)	Gynaecological epithelial malignant neoplasms	First-generation taxoid medicines	Likely ineffective
		Ecteinascidin medicinal products	Likely ineffective
Endometrial carcinoma	Gynaecological epithelial malignant neoplasms	First-generation taxoid medicinal products	Likely ineffective
		Ecteinascidin medicinal products	Likely ineffective

<b>Condition in previous class condition waiver</b>	<b>Groups of condition or condition referred to in revised class waiver</b>	<b>Class(es) of medicinal product referred to in revised class waiver</b>	<b>Scientific assessment conclusion</b>
Peritoneal carcinoma (excluding blastomas and sarcomas)	Gynaecological epithelial malignant neoplasms	First-generation taxoid medicinal products Ecteinascidin medicinal products	Likely ineffective  Likely ineffective
Prostate carcinoma (excluding rhabdomyosarcoma)	Prostate malignant neoplasms	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  First-generation taxoid medicinal products	Likely ineffective    Likely ineffective
Hairy cell leukaemia	Mature B, T and NK cell neoplasms	Primarily alkylating medicinal products  Retinoic X receptor-activating medicinal products  Immunomodulatory cytokine medicinal products	Do not represent significant therapeutic benefits  Do not represent significant therapeutic benefits  Do not represent significant therapeutic benefits
Multiple myeloma	Mature B, T and NK cell neoplasms	Primarily alkylating medicinal products  Retinoic X receptor-activating medicines  Immunomodulatory cytokine medicinal products	Do not represent significant therapeutic benefits  Do not represent significant therapeutic benefits  Do not represent significant therapeutic benefits
Alzheimer's disease	Alzheimer's disease		Confirmed

<b>Condition in previous class condition waiver</b>	<b>Groups of condition or condition referred to in revised class waiver</b>	<b>Class(es) of medicinal product referred to in revised class waiver</b>	<b>Scientific assessment conclusion</b>
Vascular dementia and vascular cognitive disorder/impairment	Coronary atherosclerosis, peripheral atherosclerosis, vascular dementia and vascular cognitive disorder / impairment		Revocation
Organic amnesic syndrome (excluding amnesic syndrome caused by alcohol and other psychoactive substances)	Organic amnesic syndrome (excluding amnesic syndrome caused by alcohol and other psychoactive substances)		Confirmed
Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis		Revocation
Parkinson's disease (non-juvenile)	Parkinson disease (non-juvenile)		Revocation
Age-related macular degeneration	Age-related macular degeneration and diabetic macular oedema		Confirmed
Climacteric symptoms associated with decreased oestrogen levels, as occurring at menopause	Climacteric symptoms associated with decreased oestrogen levels, as occurring at menopause		Confirmed
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).	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)		Confirmed

<b>Condition in previous class condition waiver</b>	<b>Groups of condition or condition referred to in revised class waiver</b>	<b>Class(es) of medicinal product referred to in revised class waiver</b>	<b>Scientific assessment conclusion</b>
Liver and intrahepatic bile duct carcinoma (excluding hepatoblastoma)	Liver and intrahepatic bile duct carcinoma		Revocation
Adenocarcinoma of the pancreas	Pancreatic malignant neoplasms	First-generation taxoid medicinal products  Pyrimidine- and pyrimidine analogue-containing medicines	Likely ineffective  Do not represent significant therapeutic benefits
Gastroenteropancreatic neuroendocrine tumours (excluding neuroblastoma, neuroganglioblastoma, phaeochromocytoma)	Neuroendocrine malignant neoplasms	Androgen receptor modulators, of oestrogen receptor modulators, of growth and sex hormones as well as their releasing or inhibiting factors, and of sex hormone-metabolism modulators  Immunomodulatory cytokine medicinal products	Likely ineffective  Do not represent significant therapeutic benefits
Gastric carcinoids	Neuroendocrine malignant neoplasms	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  Immunomodulatory cytokine medicinal products	Likely ineffective  Do not represent significant therapeutic benefits
Adenocarcinoma of the colon and rectum	Intestinal malignant neoplasms	First-generation taxoid medicinal products  Her- / epidermal growth factor-receptor antibody medicinal products	Likely ineffective  Likely ineffective

Condition in previous class condition waiver	Groups of condition or condition referred to in revised class waiver	Class(es) of medicinal product referred to in revised class waiver	Scientific assessment conclusion
		<p>Thymidylate synthase inhibitor medicinal products</p> <p>First- and second generation platinum-containing medicinal products</p> <p>Pyrimidine- and pyrimidine analogue-containing medicinal products</p>	<p>Likely ineffective</p> <p>Do not represent significant therapeutic benefits</p> <p>Do not represent significant therapeutic benefits</p>
Ureter and bladder carcinoma	Ureter and bladder carcinoma	First- and second generation platinum-containing medicinal products	Do not represent significant therapeutic benefits
Kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney)	Kidney and renal pelvis carcinoma		Revocation
Vaginal and vulvar carcinoma (excluding rhabdomyosarcoma and soft tissue sarcoma)	Gynaecological malignant neoplasms	<p>First-generation taxoid medicinal products</p> <p>Ecteinascidin medicinal products</p>	<p>Likely ineffective</p> <p>Likely ineffective</p>
Melanoma (from 0 to less than 12 years)	Skin malignant neoplasm	<p>Pyrimidine- and pyrimidine analogue-containing medicinal products</p> <p>Alkylating-methylating medicinal products</p> <p>Immunomodulatory cytokine medicinal products</p>	<p>Do not represent significant therapeutic benefits</p> <p>Do not represent significant therapeutic benefits</p> <p>Do not represent significant therapeutic benefits</p>

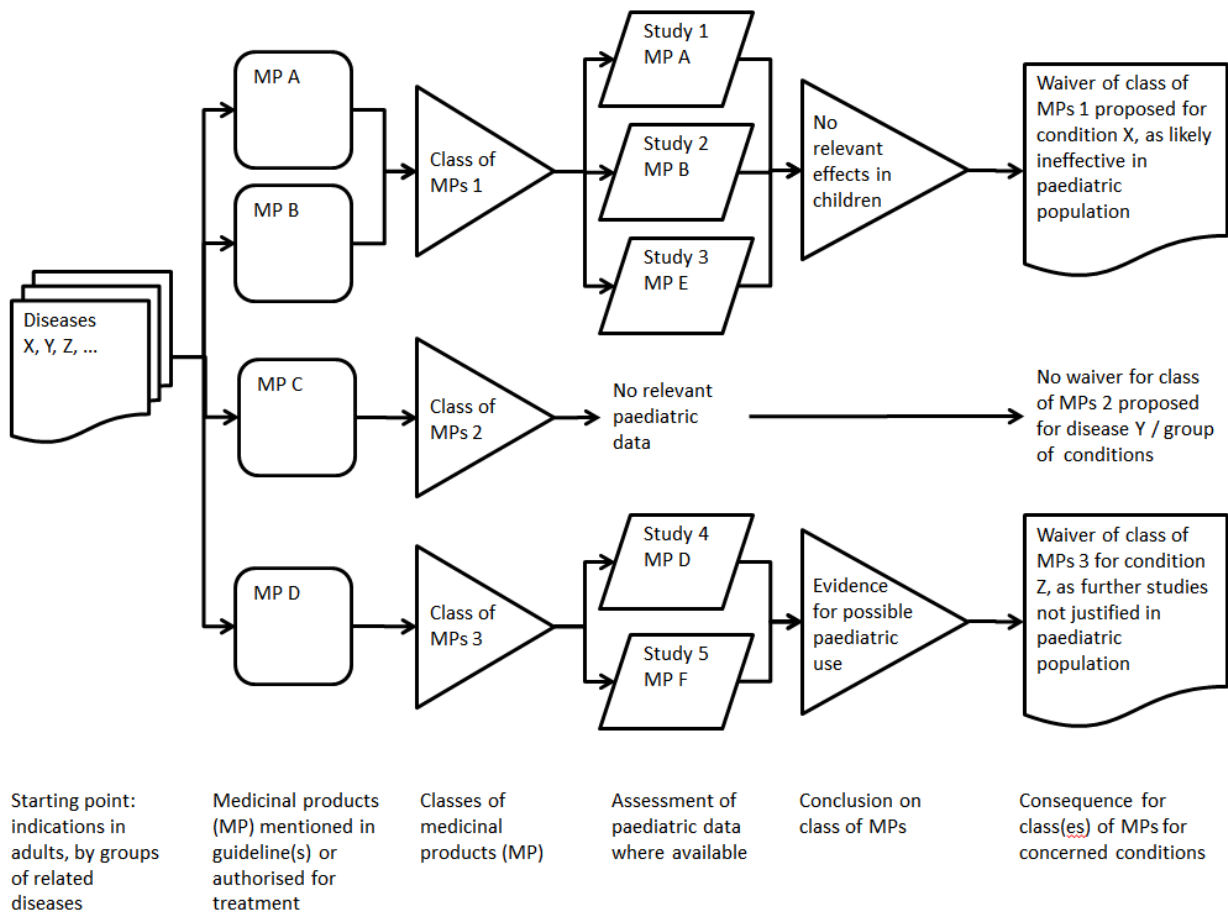


<b>Condition in previous class condition waiver</b>	<b>Groups of condition or condition referred to in revised class waiver</b>	<b>Class(es) of medicinal product referred to in revised class waiver</b>	<b>Scientific assessment conclusion</b>
Gastric adenocarcinoma	Intestinal malignant neoplasms	<p>First-generation taxoid medicinal products</p> <p>Her- / epidermal growth factor-receptor antibody medicinal products</p> <p>Thymidylate synthase inhibitor medicinal products</p> <p>First- and second generation platinum-containing</p> <p>Pyrimidine- and pyrimidine analogue-containing medicinal products</p>	<p>Likely ineffective</p> <p>Likely ineffective</p> <p>Likely ineffective</p> <p>Do not represent significant therapeutic benefits</p> <p>Do not represent significant therapeutic benefits</p>
Chronic lymphocytic leukaemia	Mature B, T and NK cell neoplasms	<p>Primarily alkylating medicinal products</p> <p>Retinoic X receptor-activating medicinal products</p> <p>Do not represent significant therapeutic benefits</p>	<p>Do not represent significant therapeutic benefits</p> <p>Do not represent significant therapeutic benefits</p> <p>Do not represent significant therapeutic benefits</p>
Cervix and corpus uteri carcinoma	Gynaecological epithelial malignant neoplasms	<p>First-generation taxoid medicinal products</p> <p>Ecteinascidin medicinal products</p>	<p>Likely ineffective</p> <p>Likely ineffective</p>
Follicular lymphoma	Mature B, T and NK cell neoplasms	<p>Primarily alkylating medicinal products</p> <p>Retinoic X receptor-activating medicinal products</p> <p>Immunomodulatory cytokine medicinal products</p>	<p>Do not represent significant therapeutic benefits</p> <p>Do not represent significant therapeutic benefits</p> <p>Do not represent significant therapeutic benefits</p>

<b>Condition in previous class condition waiver</b>	<b>Groups of condition or condition referred to in revised class waiver</b>	<b>Class(es) of medicinal product referred to in revised class waiver</b>	<b>Scientific assessment conclusion</b>
Primary and secondary osteoarthritis	Primary and secondary osteoarthritis		Confirmed
Coronary atherosclerosis	Coronary atherosclerosis, peripheral atherosclerosis, vascular dementia and vascular cognitive disorder / impairment		Revocation
Peripheral atherosclerosis	Coronary atherosclerosis, peripheral atherosclerosis, vascular dementia and vascular cognitive disorder / impairment		Revocation
Huntington chorea	Huntington chorea		Revocation
Benign prostatic hyperplasia	Benign prostatic hyperplasia	Androgen antagonist medicinal products	Do not represent significant therapeutic benefits
Erectile dysfunction	Erectile dysfunction		Confirmed
Primary gout (excluding Lesch-Nyhan syndrome and other secondary forms of gout)	Primary gout	Colchicum alkaloid (colchicine and its derivatives) medicinal products	Do not represent significant therapeutic benefits
Primary myelofibrosis	Myeloproliferative neoplasms	Ribonucleotide reductase beta-2 inhibitor medicinal products  Primarily alkylating medicinal products  Immunomodulatory cytokine medicinal products	Do not represent significant therapeutic benefits  Do not represent significant therapeutic benefits  Do not represent significant therapeutic benefits
Diabetic macular oedema	Age-related macular degeneration and diabetic macular oedema		Confirmed

Condition in previous class condition waiver	Groups of condition or condition referred to in revised class waiver	Class(es) of medicinal product referred to in revised class waiver	Scientific assessment conclusion
Mesothelioma	Lung malignant neoplasms	First-generation taxoid medicinal products  Thymidylate synthase inhibitor medicinal products	Likely ineffective  Likely ineffective
Actinic keratosis	Actinic keratosis	Pyrimidine- and pyrimidine analogue-containing medicines	Do not represent significant therapeutic benefits
Vulvar intraepithelial neoplasia	Vulvar intraepithelial neoplasia		Confirmed

## Revision



Schematic representation of methodological aspects of the class waiver revision

## 5. References

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