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Evaluation of carcinogenicity studies of medicinal products for human use authorised via the European centralised procedure (1995–2009)

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ABSTRACT

Carcinogenicity data of medicinal products for human use that have been authorised via the European centralised procedure (CP) between 1995 and 2009 were evaluated. Carcinogenicity data, either from long-term rodent carcinogenicity studies, transgenic mouse studies or repeat-dose toxicity studies were available for 144 active substances contained in 159 medicinal products. Out of these compounds, 94 (65%) were positive in at least one long-term carcinogenicity study or in repeat-dose toxicity studies. Fifty compounds (35%) showed no evidence of a carcinogenic potential. Out of the 94 compounds with positive findings in either carcinogenicity or repeat-dose toxicity studies, 33 were positive in both mice and rats, 40 were positive in rats only, and 21 were positive exclusively in mice. Long-term carcinogenicity studies in two rodent species were available for 116 compounds. Data from one long-term carcinogenicity study in rats and a transgenic mouse model were available for eight compounds. For 13 compounds, carcinogenicity data were generated in only one rodent species. One compound was exclusively tested in a transgenic mouse model. Six compounds were tumourigenic in repeat-dose toxicity studies in rats.

The majority of tumour findings observed in rodent carcinogenicity studies were considered not to be relevant for humans, either due to a rodent-specific mechanism of carcinogenicity, a high safety margin between exposures at the NOAEL (No Observed Adverse Effect Level) in rodents and recommended therapeutic doses in humans, or based on historical control data, a small effect size and lack of dose–response relationship and tumours typically observed in rodent strains used, or were considered not to be relevant for humans based on literature and clinical data or likely differences in metabolism/local concentrations between rodents and humans.

Due to the high number of rodent tumour findings with unlikely relevance for humans, the value of the currently used testing strategy for carcinogenicity appears questionable. A revision of the carcinogenicity testing paradigm is warranted.

1. Introduction

1.1. Marketing authorisation of pharmaceuticals for human use in Europe

In the European Economic Area (EEA),[1] a marketing authorisation (MA) can either be issued by the competent authority of a Member State (or EEA country) for its own territory (national authorisation) or for the entire Community (Community authorisation). Regulation (EC) No. 726/2004 of the European Parliament and of the Council lays down a centralised Community procedure for the authorisation of medicinal products, for which there is a single application to the European Medicines Agency (EMA), a single evaluation by the Committee for Medicinal Products for Human Use (CHMP) within the EMA and a single marketing authorisation granted by the European Commission (EC). Community authorisations can be granted for medicinal products that fall under the mandatory scope of the centralised procedure which includes medicinal products derived from biotechnology, new active substances for which the therapeutic indication is the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder, diabetes, auto-immune diseases or viral diseases, and applications for medicinal products designated as orphan medicinal products. Other new active substances may be accepted for consideration under the centralised procedure when the applicant shows that a new active substance or the medicinal product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a Community authorisation for the medicinal product is in the interests of patients at Community level (optional scope of the centralised procedure). Generic applications of medicinal products authorised

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[1] Member States of the European Union plus Norway, Iceland and Liechtenstein.

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via the centralised procedure may also be authorised via the centralised procedure.

1.2. Carcinogenicity testing of pharmaceuticals for human use

1.2.1. Objective of carcinogenicity testing

The objective of carcinogenicity studies is to determine whether a pharmaceutical is tumourigenic in animals and whether this tumourigenic potential poses a relevant risk to humans (ICH S1A guideline; CPMP note for guidance on carcinogenic potential).

1.2.2. Need for carcinogenicity studies

Carcinogenicity studies are generally required for pharmaceuticals which are expected to be used continuously for at least six months or intermittently for the treatment of chronic or recurrent conditions (ICH S1A guideline).

Carcinogenicity studies are also necessary if there is a concern about the carcinogenic potential of a pharmaceutical. Relevant factors include: (1) previous demonstration of carcinogenic potential in the product class that is considered relevant to humans, (2) structure–activity relationship suggesting a carcinogenic risk, (3) positive genotoxicity findings, (4) evidence of preneoplastic lesions in repeat-dose toxicity studies, and (5) long-term tissue retention of the pharmaceutical or its metabolite(s) resulting in local tissues reactions or pathophysiological responses (ICH S1A guideline).

Pharmaceutical administered infrequently or for short duration, e.g. anaesthetics and radiolabelled imaging agents do not need carcinogenicity studies unless there is a cause for concern (ICH S1A guideline).

Carcinogenicity studies are also not required for therapeutics intended to treat patients with advanced cancer who have a short life-expectancy, for pharmaceuticals administered by the dermal or topical route, unless there is significant systemic exposure, and for biotechnology-derived pharmaceuticals, such as endogenous peptides and proteins especially when they are given as replacement therapy (ICH S1A guideline; ICH S9 guideline; ICH S6 guideline).

1.2.3. Test systems for carcinogenicity

1.2.3.1. Traditional approach. Long-term carcinogenicity studies in rodents have been required since the 1970s for marketing authorisation of pharmaceuticals in Europe, the USA and Japan. The studies have traditionally been conducted in mice and rats using life-time treatment.

Until now, the traditional approach of conducting long-term carcinogenicity studies in mice and rats has remained the most frequently chosen testing strategy. However, discussions have been ongoing for many years whether a single study alone would be adequate for assessing the carcinogenic potential of pharmaceuticals.

1.2.3.2. Alternative approach. The analysis of several databases did not support the concept of conducting long-term carcinogenicity in two rodent species. Positive carcinogenicity findings were often not relevant to humans. These analyses led to the introduction by ICH of a more flexible weight of evidence approach for carcinogenicity testing, that is the use of scientific judgement in the evaluation of the data derived from one long-term carcinogenicity study along with other appropriate investigations (Smith, 1996; ICH S1B guideline).

According to the ICH S1B guideline, one long-term carcinogenicity study should be supplemented by another study that supplements the long-term carcinogenicity study and provides information that is not readily available from the long-term assay. Appropriate experimental models include short or medium term *in vivo* rodent assays such as the p53+/− deficient mouse model or the TgHras2 mouse model.

The ICH S1B guideline recommends that a single long-term study (usually in the rat) should be conducted and should be complemented by a short- or medium-term *in vivo* rodent study. The short or medium-term test should provide additional information that is not readily available from the long-term assay. Usually the mouse is the preferred species to be used in a short or medium-term assay, especially when the rat is used in the long-term study.

Several transgenic mouse assays have proven useful for replacement of the second long-term study and are generally accepted by regulatory authorities in all ICH regions. Among these are the p53+/− deficient model, the TgHras2 model and the Tg.AC model. The regulatory authority concerned should always be consulted before a decision on the choice of a particular model is made.

1.2.3.3. Toxicokinetic studies. Toxicokinetic assessments are an essential component of carcinogenicity studies. They allow to relate systemic exposure levels to the toxic and/or carcinogenic findings observed in carcinogenicity studies and to contribute to the assessment of the relevance of these findings to clinical safety (ICH S3A guideline).

1.2.3.4. Mechanistic studies. Mechanistic studies are useful for the interpretation of tumour findings in a carcinogenicity study and can provide a perspective of their relevance to human risk assessment (ICH S1B guideline). As such, mechanistic studies are often provided for compounds with positive carcinogenicity findings. For example, the measurement of hormone levels, such as thyroxine or prolactin, have been used to confirm species- or rodent-specific hormonal imbalances and related tumour development induced by test compounds (ICH S1B guideline). Additional genotoxicity tests, such as the UDS test or the Comet assay, or additional studies in transgenic or neonatal mice have been used for compounds with equivocal findings in the standard battery for genotoxicity testing (ICH S2B guideline) in order to exclude a genotoxic mechanism of carcinogenicity.

1.2.3.5. Photocarcinogenicity studies. The SKH1 (hr/hr) albino hairless mouse model is currently the most widely used model to assess photocarcinogenicity in animals (CPMP note for guidance on photosafety testing). The model is designed to induce squamous cell carcinoma and their precursors by chronic UV radiation in all animals and to assess the effect of simultaneously applied test substances on the time to tumour development. The model is being used to assess the co-carcinogenic potential of dermally applied products that intended for long-term or chronically intermittent treatment of skin disorders. However, the predictivity of the albino hairless mouse model for the human situation is at present unclear (CPMP note for guidance on photosafety testing).

2. Methods

This paper presents an evaluation of carcinogenicity data of medicinal products for human use that have been authorised via the European centralised procedure (CP) between 1995 and 2009. Data were retrieved from European Public Assessment Reports (EPARs) and Summary of Product Characteristics (SPCs) as the publicly available sources of scientific and labelling information on the website of the European Medicines Agency (EMA). Additional information on the approved products that is eventually available from the scientific literature was beyond the scope of this evaluation.

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Table 1
Reference medicinal products which were tested for carcinogenicity.

Reference medicinal product	ATC code	International nonproprietary name (INN)	Pharmacotherapeutic group	Results of genotoxicity studies	Results of carcinogenicity studies	
					Mouse	Rat
ATC code ADrugs acting on the gastrointestinal system and on the metabolism						
ATC code A02 Drugs for acid related disorders						
Pantozol control	A02BC02	Pantoprazole	Proton pump inhibitors	Not genotoxic	Positive	Positive
ATC code A03 Drugs for functional gastrointestinal disorders						
Resolor	A03AE04	Prucalopride	Drugs acting on serotonin receptors	Not genotoxic (mutagenic in Ames test in TA100 strain)	Positive	Positive
ATC code A04 Anti-emetics and anti-nauseants						
Aloxi	A04AA05	Palonosetron	Antiemetics and antinauseants, serotonin (5HT3) antagonists	Not genotoxic	Negative	Positive
Emend	A04AD12	Aprepitant	Antiemetics and antinauseants	Not genotoxic	Negative	Positive
ATC code A08 Anti-obesity preparations, excluding diet products						
Xenical	A08AB01	Orlistat	Anti-obesity agents	Not genotoxic	Negative	Negative
ATC code A10 Drug used in diabetes						
Lantus	A10AE04	Insulin glargine	Insulins and analogues for injection, long-acting	Not genotoxic	Positive	Positive
Avandamet	A10BD03	Rosiglitazone/metformin	Combinations of oral blood glucose lowering medicinal products	Rosiglitazone not genotoxic Metformin not gneotoxic	Rosiglitazone negative Metformin negative	Rosiglitazone positive (benign lipoma) Metformin positive (benign uterus polyps)
Avaglim	A10BD04	Rosiglitazone/glimepiride		Rosiglitazone not genotoxic Glimepiride not genotoxic	Rosiglitazone negative (positive in APCmin model) Glimepiride positive	Rosiglitazone positive Glimipiride positive
Competact	A10BD05	Pioglitazone/metformin		Pioglitazone not genotoxic Metformin not genotoxic	Pioglitazone negative Metformin negative	Pioglitazone positive Metformin positive
Tandemact	A10BD06	Pioglitazone/glimepiride		Pioglitazone not genotoxic Glimepiride not genotoxic	Pioglitazone negative Glimepiride positive	Pioglitazone positive Glimepiride positive
Efficib	A10BD07	Sitagliptin/metformin		Sitagliptin not genotoxic Metformin not genotoxic	Sitagliptin negative Metformin negative	Sitagliptin positive Metformin positive
Eucreas	A10BD08	Vildagliptin/metformin		Vildagliptin not genotoxic Metformin not genotoxic	Vildagliptin positive Metformin negative	Vildagliptin negative Metformin positive
Avandia	A10BG02	Rosiglitazone	Oral blood glucose lowering drugs; thiazolidinediones	Not genotoxic	Negative	Positive
Glustin	A10BG03	Pioglitazone		Not genotoxic	Negative	Positive
Xelevia	A10BH01	Sitagliptin	Dipeptidyl peptidase 4 (DPP-4) inhibitors	Not genotoxic	Negative	Positive
Galvus	A10BH02	Vildagliptin		Not genotoxic	Positive	Negative
Onglyza	A10BH03	Saxagliptin		Not genotoxic	Negative	Negative
NovoNorm	A10BX02	Repaglinide	Other blood glucose lowering drugs excluding insulins	Not genotoxic	Negative	Positive
Starlix	A10BX03	Nateglinide		Not genotoxic	Negative	Negative
Byetta	A10BX04	Exenatide		Not genotoxic	Negative	Positive
Victoza	A10BX07	Liraglutide		Not genotoxic	Positive	Positive
ATC code A16 Other alimentary tract and metabolism products						
Zavesca	A16AX06	Miglustat	Other alimentary tract and metabolism products	Not genotoxic	Positive	Positive
Kuvan	A16AX07	Sapropterin		Genotoxic (*in vitro*)	Negative	Negative
ATC code B Blood and blood forming organs						
ATC code B01 Anti-thrombotic agents						
Plavix	B01AC04	Clopidogrel	Platelet aggregation inhibitors excluding heparin	Not genotoxic	Negative	Negative
Ventavis	B01AC11	Iloprost		Not genotoxic	Negative	Negative
Efient	B01AC22	Prasugrel		Not genotoxic	Positive	Negative

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Table 1 (*continued*)

Reference medicinal product	ATC code	International nonproprietary name (INN)	Pharmacotherapeutic group	Results of genotoxicity studies	Results of carcinogenicity studies	
					Mouse	Rat
ATC code C Cardiovascular system						
ATC code C01 Cardiac therapy						
Corlentor	C01EB17	Ivabradine	Other cardiac preparations	Not genotoxic	Negative	Negative
Ranexa	C01EB18	Ranolazine		Not genotoxic (clastogenic in chromosomal aberration test)	Negative	Positive
ATC code C02 Anti-hypertensives						
Polaris	C02KX02	Ambrisentan	Other antihypertensives	Not genotoxic	Negative	Negative
Tracleer	C02KX01	Bosentan		Not genotoxic	Positive	Positive
Thelin	C02KX03	Sitaxentan sodium		Not genotoxic (clastogenic *in vitro* at cytotoxic concentrations)	p53+/− model negative	Positive
ATC code C03 Diuretics						
Samsca	C03XA01	Tolvaptan	Vasopressin antagonists	Not genotoxic	Negative	Negative
ATC code C09 Agents acting on the renin-angiotensin system						
Aprovel	C09CA04	Irbesartan	Angiotensin II antagonists	Not genotoxic	Negative	Negative
Micardis	C09CA07	Telmisartan		Not genotoxic	Negative	Negative
CoAprovel	C09DA04	Irbesartan/ hydrochlorothiazide	Angiotensin II antagonists, combinations	Hydrochlorothiazide equivocal	Irbesartan negative hydrochlorothiazide positive	Irbesartan negative hydrochlorothiazide negative
Micardis Plus	C09DA07	Telmisartan/ hydrochlorothiazide	Angiotensin II antagonists, diuretics	Telmisartan not genotoxic hydrochlorothiazide equivocal	Telmisartan negative hydrochlorothiazide positive	Telmisartan negative hydrochlorothiazide negative
Exforge	C09DB01	Amlodipine besylate/ valsartan	Calcium channel blockers, angiotensin II antagonists	Amlodipine not genotoxic Valsartan not genotoxic	Amlodipine negative Valsartan negative	Amlodipine negative valsartan negative
Exforge HCT	C09DX01	Amlodipine besylate/ valsartan/ hydrochlorothiazide	Angiotensin II antagonists, plain (valsartan), combinations with dihydropyridine derivatives (amlodipine) and thiazide diuretics (hydrochlorothiazide)	Amlodipine not genotoxic Valsartan not genotoxic Hydrochlorothiazide equivocal	Amlodipine negative Valsartan negative Hydrochlorothiazide positive	Amlodipine negative valsartan negative hydrochlorothiazide negative
Riprazo	C09XA02	Aliskiren	Renin inhibitors	Not genotoxic	Alternative model negative	Negative
Rasilez HCT		Aliskiren hemifumarate/ hydrochlorothiazide	Renin inhibitors, combinations with diuretics	Aliskrien not genotoxic hydrochlorothiazide equivocal	Aliskrien alternative model negative Hydrochlorothiazide positive	Aliskrien negative hydrochlorothiazide negative
ATC code C10 Lipid modifying agents						
Cholestagel	C10AC04	Colesevelam	Bile acid sequestrants	Not genotoxic	Negative (low survival rate)	Positive
Tredaptive	C10AD52	Nicotinic acid/laropiprant	Nicotinic acid and derivatives	Nicotinic acid not genotoxic (literature) laropiprant not genotoxic	Nicotinic acid negative (literature) laropiprant positive	Nicotinic acid negative (literature) laropiprant negative
ATC code D Dermatologicals						
ATC code D06 Antibiotics and chemotherapeutics for dermatological use						
Aldara	D06BB10	Imiquimod	Chemotherapeutics for topical use, antiviral	Not genotoxic	Topical negative	Not performed
ATC code D11 Other dermatological preparations						
Protopic	D11AX14	Tacrolimus	Other dermatologicals	Not genotoxic	Topical positive PhotoCA positive oral negative	Topical not performed oral negative
Vaniqa	D11AX16	Eflornithine		Not genotoxic	Topical negative photoCA negative oral negative	Topical not performed oral negative
ATC code G Genito-urinary system and sex hormones						
ATC code G02 Other gynecologicals						
Tractocile	G02CX01	Atosiban	Other gynaecologicals	Not genotoxic	Not performed	Positive
ATC code G03 Sex hormones and modulators of the genital system						
EVRA	G03AA13	Norelgestromin/ethinyl estradiol	Norelgestromin and estrogen	Norelgestromin not genotoxic ethinyl estradiol not genotoxic	Not performed	Combination of norgestimate and ethinyl estradiol positive combination negative in a 10-year monkey

Table 1 (*continued*)

Reference medicinal product	ATC code	International nonproprietary name (INN)	Pharmacotherapeutic group	Results of genotoxicity studies	Results of carcinogenicity studies	
					Mouse	Rat
						study
Evista	G03XC01	Raloxifene hydrochloride	Selective oestrogen receptor modulator (SERM)	Not genotoxic	Negative	Negative
Fablyn	G03XC01	Lasofoxifene		Not genotoxic	Positive	Positive
Conbriza	G03XC02	Bazedoxifene		Not genotoxic	TgHras2 model positive	Positive
ATC code G04 Urologicals						
Emselex	G04BD10	Darifenacin	Urinary antispasmodics	Not genotoxic	Negative	Positive (considered not treatment-related)
Toviaz	G04BD11	Fesoterodine		Not genotoxic	Negative	Negative
Viagra Revatio	G04BE03	Sildenafil	Drugs used in erectile dysfunction	Not genotoxic	Negative	Negative
Cialis	G04BE08	Tadalafil		Not genotoxic	Negative (numerical increase)	Negative (numerical increase)
Levitra	G04BE09	Vardenafil		Not genotoxic	Negative	Negative
ATC code H Systemic hormonal preparations, excluding sex hormones and insulins						
ATC code H01 Pituitary and hypothalamic hormones and analogues						
Increlex	H01AC03	Mecasermin	Somatropin and somatropin agonists	Not genotoxic	Not performed	Positive
ATC code H05 Calcium homeostasis						
Forsteo	H05AA02	Teriparatide	Parathyroid hormones and analogues	Not genotoxic	Not performed	Positive
Preotact	H05AA03	Parathyroid hormone (rDNA)		Not genotoxic	Not performed	Positive
Mimpara	H05BX01	Cinacalcet	Anti-parathyroid agents	Not genotoxic	Negative	Negative
ATC code J Anti-infectives for systemic use						
ATC code J02 Anti-mycotics for systemic use						
Vfend	J02AC03	Voriconazole	Triazole derivatives	Not genotoxic	Positive	Positive
Noxafil	J02AC04	Posaconazole		Not genotoxic	Negative	Positive
ATC code J05 Antivirals for systemic use						
Rebetol	J05AB04	Ribavirin	Nucleosides and nucleotides excluding reverse transcriptase inhibitors	Genotoxic	Negative	Positive (upper range of historical controls)
Invirase	J05AE01	Saquinavir	Protease inhibitors	Not genotoxic	Negative	Negative
Crixivan	J05AE02	Indinavir		Not genotoxic	Negative	Positive
Norvir	J05AE03	Ritonavir		Not genotoxic	Positive	Negative
Viracept	J05AE04	Nelfinavir		Not genotoxic	Negative	Positive
Agenerase	J05AE05	Amprenavir		Not genotoxic	Positive	Positive
Kaletra	J05AE06	Lopinavir/Ritonavir		Not genotoxic	Combination positive	Combination negative
Telzir	J05AE07	Fosamprenavir		Not genotoxic	Positive	Positive
Reyataz	J05AE08	Atazanavir sulphate		Not genotoxic (clastogenic in chromo-somal aberration test)	Positive	Negative
Aptivus	J05AE09	Tipranavir		Not genotoxic	Positive	Positive
Prezista	J05AE10	Darunavir		Not genotoxic	Positive	Positive
Zerit	J05AF04	Stravudine	Nucleoside and nucleotide reverse transcriptase inhibitors	Genotoxic	Positive	Positive
Epivir	J05AF05	Lamivudine		Genotoxic	Negative	Negative
Ziagen	J05AF06	Abacavir sulphate		Genotoxic	Positive	Positive
Viread	J05AF07	Tenofovir disoproxil		Genotoxic	Positive	Positive (benign lipoma, within historical control range)
Hepsera	J05AF08	Adefovir dipivoxil		Genotoxic	Negative	Negative
Emtriva	J05AF09	Emtricitabine		Not genotoxic	Negative	Negative
Baraclude	J05AF10	Entecavir		Genotoxic (clastogenic in chromo-somal aberration test)	Positive	Positive
Sebivo	J05AF11	Telbivudine		Not genotoxic	TgHras2 model negative	Positive
Viramune	J05AG01	Nevirapine		Not genotoxic	Positive	Positive

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Table 1 (*continued*)

Reference medicinal product	ATC code	International nonproprietary name (INN)	Pharmacotherapeutic group	Results of genotoxicity studies	Results of carcinogenicity studies	
					Mouse	Rat
Stocrin	J05AG03	Efavirenz	Non-nucleoside reverse transcriptase inhibitors	Not genotoxic	Positive	Negative
Intelence	J05AG04	Etravirine		Not genotoxic	Positive	Negative
Tamiflu	J05AH02	Oseltamivir	Neuraminidase inhibitors	Not genotoxic	Negative Dermal Tg.AC model negative	Positive (trend)
Combivir	J05AR01	Lamivudine/zidovudine	Antivirals for treatment of HIV infections, combinations	Lamivudine genotoxic Zidovudine genotoxic	Lamivudine negative zidovudine positive	Lamivudine negative Zidovudine positive
Kivexa	J05AR02	Abacavir sulphate/ lamivudine		Abacavir genotoxic lamuvudine genotoxic	Abacavir positive lamivudine negative	Abacavir positive Lamivudine negative
Truvada	J05AR03	Emtricitabine/tenofovir disoproxil		Emtricitabine not genotoxic Tenofovir genotoxic	Emtricitabine negative tenofovir positive	Emtricitabine negative Tenofovir negative
Trizivir	J05AR04	Abacavir sulphate/ lamivudine/zidovudine		Lamivudine genotoxic zidovudine genotoxic abacavir genotoxic	Lamivudine negative zidovudine positive abacavir positive	Lamivudine negative zidovudine positive abacavir positive
Atripla	J05AR06	Efavirenz/emtricitabine/ tenofovir disoproxil		Efavirenz not genotoxic emtricitabine not genotoxic tenofovir genotoxic	Efavirenz positive emtricitabine negative tenofovir positive	Efavirenz negative emtricitabine negative tenofovir negative
Isentress	J05AX08	Raltegravir	Other antivirals	Not genotoxic	Negative	Negative
Celsentri	J05AX09	Maraviroc		Not genotoxic	TgHras2 model negative	Positive
ATC code L Anti-neoplastic and immunomodulating agents						
ATC code L01 Anti-neoplastic agents						
Xeloda	L01BC06	Capecitabine	Antimetabolites	Genotoxic	Negative	Not performed
Iressa	L01XE02	Gefitinib	Protein kinase inhibitors	Not genotoxic	Positive	Positive
Afinitor	L01XE10	Everolimus		Not genotoxic	Positive	Negative
Onsenal	L01XX33	Celecoxib	Other antineoplastic agents	Not genotoxic	Positive (within historical control values)	Positive (within historical control values)
ATC code L02 Endocrine therapy						
Fareston	L02BA02	Toremifene	Anti-oestrogens	Not genotoxic	Positive	Negative
Faslodex	L02BA03	Fulvestrant		Not genotoxic	Positive (literature)	Positive
Firmagon	L02BX02	Degarelix	Other hormone antagonists and related agents	Not genotoxic	Positive	Positive
ATC code L04 Immunosuppressants						
CellCept	L04AA06	Mycophenolate mofetil	Selective immunosuppressive agents	Genotoxic	Negative	Negative
Arava	L04AA13	Leflunomide		Leflunomide not genotoxic minor metabolite genotoxic *in vitro*	Positive	Negative
Rapamune	L04AA10	Sirolimus	Calcineurin inhibitors	Not genotoxic	Positive	Positive
Orencia	L04AA24	Abatacept		Not genotoxic	Positive	Not performed
Advagraf	L04AD02	Tacrolimus		Not genotoxic	Oral negative topical not performed	Oral negative topical positive
Modigraf	L04AD02	Tacrolimus	Other immunosuppressive agents	Not genotoxic	Oral negative topical not performed	Oral negative topical positive
Thalidomide Celgene	L04AX02	Thalidomide		Not genotoxic	Negative	Negative
ATC code M Musculo-skeletal system						
ATC code M05 Drugs for treatment of bone diseases						
Zometa	M05BA08	Zoledronic acid	Bisphosphonates	Not genotoxic	Positive	Negative
Bondenza	M05BA06	Ibandronic acid		Not genotoxic	Negative	Negative
Fosavance	M05BB03	Alendronate sodium/ Colecalciferol	Bisphosphonates, combinations	Alendronate not genotoxic Colecalciferol not genotoxic	Alendronate negative colecalciferol not performed	Alendronate negative colecalciferol not performed
Osigraft	M05BC02	Eptotermin alfa	Bone morphogenetic protein	Not genotoxic *(in vitro)*	Not performed	Positive

Table 1 (*continued*)

Reference medicinal product	ATC code	International nonproprietary name (INN)	Pharmacotherapeutic group	Results of genotoxicity studies	Results of carcinogenicity studies	
					Mouse	Rat
Osseor	M05BX03	Strontium ranelate	Other drugs affecting bone structure and mineralisation	Not genotoxic	Negative	Positive
ATC code N Nervous system						
ATC code N01 Anesthetics						
Qutenza	N01BX04	Capsaicin	Other local anesthetics	Not genotoxic (weakly positive in mouse lymphoma assay)	Dermal Tg.AC model negative	Not performed
ATC code N03 Anti-epileptics						
Inovelon	N03AF03	Rufinamide	Carboxamide derivatives	Not genotoxic	Positive	Negative
Exalief	N03AF04	Eslicarbazepine acetate		Not genotoxic (clastogenic in some *in vitro* assays)	Positive	Not performed
Keppra	N03AX14	Levetiracetam	Other antiepileptics	Not genotoxic	Negative	Negative
Zonegran	N03AX15	Zonisamide		Not genotoxic	Negative	Negative
Lyrica	N03AX16	Pregabalin		Not genotoxic	Positive	Negative
Diacomit	N03AX17	Stiripentol		Not genotoxic (clastogenic *in vitro* at cytotoxic concentrations)	Positive	Negative
Vimpat	N03AX18	Lacosamide		Not genotoxic (clastogenic in mouse lymphoma assay)	Negative	Negative
ATC code N04 Anti-Parkinson drugs						
Stalevo	N04BA03	Levodopa/carbidopa/ entacapone	Dopa and dopa derivatives	Entacapone genotoxic (clatogenic *in vitro*) levodopa/Carbidopa not genotoxic (literature)	Entacapone negative levodopa/carbidopa not performed	Entacapone positive levodopa/carbidopa negative (literature)
Sifrol	N04BC05	Pramipexole	Dopamine agonists	Not genotoxic	Negative	Positive
Neupro	N04BC09	Rotogotine		Not genotoxic (clastogenic in mouse lymphoma assay)	Negative	Positive
Azilect	N04BD02	Rasagiline	Monoamine oxidase B inhibitors	Genotoxic (clastogenic *in vitro*)	Positive	Negative
Tasmar	N04BX01	Tolcapone	Anti-Parkinson agents	Not genotoxic	Negative	Positive
Comtess	N04BX02	Entacapone		Genotoxic (clastogenic *in vitro*)	Negative	Positive
ATC code N05 Psycholeptics						
Zyprexa	N05AH03	Olanzapine	Diazepines, oxazepines and thiazepines	Not genotoxic	Positive	Positive
Zypadhera	N05AH03	Olanazapine		Not genotoxic	Depot form not performed (technical reasons)	Depot form negative
Abilify	N05AX12	Aripiprazole	Other antipsychotics	Not genotoxic	Positive	Positive
Invega	N05AX13	Paliperidone		Not genotoxic	Positive	Positive
Zerene	N05CF03	Zaleplon	Benzodiazepine related drugs	Not genotoxic	Negative	Negative
Circadin	N05CH01	Melatonin	Melatonin receptor agonists	Not genotoxic	Tg NK model negative	Positive
ATC code N06 Psychoanaleptics						
Exelon	N06DA03	Rivastigmine	Anticholinesterases	Not genotoxic	Negative	Negative
Ariclaim	N06AX21	Duloxetine	Other antidepressants	Not genotoxic	Negative	Negative (multinucleated liver cells)
Thymanax	N06AX22	Agomelatine		Not genotoxic (clastogenic in chromosomal aberration test)	Positive	Positive
Ebixa	N06DX01	Memantine	Other anti-dementia drugs	Not genotoxic	Negative	Negative
ATC code N07 Other nervous system drugs						
Champix	N07BA03	Varenicline tartrate	Active substances used in nicotine dependence	Not genotoxic	Negative	Positive
Suboxone	N07BC51	Buprenorphine hydrochloride/naloxone hydrochloride	Drugs used in opioid dependence	Combination not genotoxic	Not performed	Combination positive
Rilutek	N07XX02	Riluzole	Other nervous system drugs	Major active metabolite genotoxic (clastogenic *in vitro*)	Negative	Negative

(*continued on next page*)

Table 1 (*continued*)

Reference medicinal product	ATC code	International nonproprietary name (INN)	Pharmacotherapeutic group	Results of genotoxicity studies	Results of carcinogenicity studies	
					Mouse	Rat
Xyrem	N07XX04	Sodium oxybate		Not genotoxic	Sodium oxybate not performed γ-butyrolactone equivocal (NTP study)	Sodium oxybate positive (upper range historical control values) γ-butyrolactone negative
ATC code R Respiratory system						
ATC code R01 Nasal preparations						
Avamys	R01AD12	Fluticasone furoate	Corticosteroids	Not genotoxic	Intransal negative	Intransal negative
ATC code R06 Antihistamines for systemic use						
Aerinaze	R06AX27; R01BA52	Desloratadine and Pseudoephedrine (as sulphate)	Antihistamines-H1 antagonist; nasal decongestants for systemic use group	Not genotoxic	Negative	Not performed
ATC code S Sensory organs						
ATC code S01 Ophthalmologicals						
Azopt	S01EC04	Brinzolamide	Antiglaucoma preparations and miotics, carbonic anhydrase inhibitors	Not genotoxic (clastogenic in mouse lymphoma assay)	Oral positive	Oral negative
DuoTrav	S01ED51	Travoprost/timolol	Antiglaucoma preparations and miotics-beta-blocking agents-timolol, combinations	Travoprost not genotoxic Timolol genotoxic (low potential)	Subcutaneous travoprost negative oral timolol positive	Subcutaneous travoprost negative oral timolol positive
Ganfort	S01ED51	Bimatoprost/timolol		Bimatoprost not genotoxic Timolol genotoxic (low potential)	Oral bimatoprost negative oral timolol positive	Oral bimatoprost negative oral timolol positive
Azarga	S01ED51	Brinzolamide/timolol		Brinzolamide not genotoxic timolol genotoxic (low potential)	Oral brinzolamide positive oral timolol positive	Oral brinzolamide negative oral timolol positive
Lumigan	S01EE03	Bimatoprost	Antiglaucoma preparations and miotics – prostaglandin analogues	Not genotoxic	Negative	Negative
Travatan	S01EE04	Travoprost		Not genotoxic	Negative	Negative
Emadine	S01GX06	Emedastine	Decongestants and antiallergics; other antiallergics	Not genotoxic	Negative (numerical increase)	Negative
Opatanol	S01GX09	Olopatadine		Not genotoxic	Negative	Negative
ATC code V Various						
ATC code V03 All other therapeutic products						
Renvela	V03AE02	Sevelamer (carbonate)	Treatment of hyperphosphataemia	Not genotoxic (clastogenic in chromosomal aberration test)	Negative (within historical control range)	Positive
Exjade	V03AC03	Deferasirox	Iron chelating agents	Not genotoxic	p53+/− model negative	Negative
Not yet classified						
Multaq	–	Dronedarone	–	Not genotoxic	Positive	Positive
Onbrez Breezhaler	–	Indacaterol	Long-acting, ß2-adrenergic agonist	Not genotoxic	TgHras2 model negative	Positive

ATC: Anatomical Therapeutic Chemical classification system.
NTP: National Toxicology Program.
PhotoCA: Photocarcinogenicity.
rDNA: Recombinant DNA.

It is important to note that this analysis is based on information available for centrally approved pharmaceuticals in the EEA and does not consider carcinogenicity studies for medicinal products that were approved via national procedures. Compounds which were tested for carcinogenicity by pharmaceutical companies but which have not been pursued or approved for marketing were also not considered in this analysis.

All medicinal products authorised via the CP between 1995 and 2009 were analysed with respect to the number of products and active substances with genotoxicity and carcinogenicity data, the tests systems used for their assessment, and the potential relevance of the data for the human situation and their impact on the labelling.

3. Results

3.1. Overview of carcinogenicity data

3.1.1. Medicinal products authorised via the centralised procedure

According to the alphabetical listing of medicinal products that have an EPAR on the EMA website, the total number of centrally authorised medicinal products until end of 2009 was 521. Out of the 521 authorised medicinal products, 146 (28%) products account for duplicate, informed consent, generic or biosimilar products, for which no new carcinogenicity data have been generated. Carcinogenicity data were available for 280 medicinal products accounting for 54% of all authorised products.

3.1.2. Fixed combination medicinal products

Fixed combinations are used in oral blood glucose lowering medicinal products, in blood pressure lowering products and topical antiglaucoma preparations (see Table 1 for reference products). All active substances contained in these fixed combination medicinal products have been individually tested for genotoxicity and carcinogenicity.

In the treatment of human immunodeficiency virus (HIV-1) infected patients, the combined use at least three active substances is currently considered essential based on the inherent high mutation rate in HIV (guideline on carcinogenicity evaluation of medicinal products for the treatment of HIV infection). Therefore, fixed combinations have been developed aiming at improving adherence by reducing pill burden (Guideline on the clinical development of medicinal products for the treatment of HIV infection) (see Table 1 for reference products). With the exception of lopinavir/ritonavir, which were tested in combination, genotoxicity and carcinogenicity studies were performed using the individual active substances. This is in accordance with the guideline on carcinogenicity evaluation of medicinal products for the treatment of HIV infection, which does not require carcinogenicity studies of drug combination, if the individual components have been adequately tested.

Active substances that have been tested for carcinogenicity in combination include norgestimate/ethinylestradiol and buprenorphin hydrochloride/naloxon hydrochloride (see Table 1 for reference products).

3.1.3. Reference medicinal products

Reference medicinal products included medicinal products containing new chemical entities (NCEs), combinations of NCEs, NCEs in combination with known active substances or products containing known active substances developed for new indications.

375 centrally authorised reference medicinal products had a valid MA a by the end of 2009. Carcinogenicity data were available for 144 individual compounds or fixed combinations that were contained in 159 reference medicinal products (Table 1). The higher number of reference medicinal products compared with the number of active substances is either due to the combination of active substances in different products, e.g. hydrochlorothiazide in combination with irbesartan (CoApprovel) and telmisartan (Micardis Plus), or due to the fact that some compounds have been approved in different indication and/or are available in different formulation, e.g. the use of sildenafil in Viagra and Revatio for the treatment of erectile dysfunction and arterial pulmonary hypertension, respectively, and the use of tacrolimus in Protopic and Advagraf for topical treatment of atopic dermatitis and systemic treatment of transplant rejection following organ transplantation, respectively.

Thus, from all reference medicinal products authorised via the CP between 1995 and 2009, carcinogenicity data have been generated for approximately 42% (159/375). Products that have not been tested for carcinogenicity include biotechnology-derived pharmaceuticals such as endogenous peptides and proteins, monoclonal antibodies and vaccines produced by recombinant DNA technology. This is consistent with current requirements (ICH S1A guideline; ICH S6 guideline). Furthermore, carcinogenicity testing is not required for products intended for short-term clinical use and for anti-neoplastic agents for the treatment of patients with short life expectancy.

Carcinogenicity studies in at least one rodent species are available for 138 compounds that were either tested individually (in the majority of cases) or in combination. Six additional compounds exhibited neoplastic lesions in repeat-dose toxicity studies and it was thus considered that carcinogenicity studies would not need to be performed for these compounds (Table 2).

Conventional long-term carcinogenicity studies in mice and rats are available for the majority of compounds, while transgenic mouse models were infrequently used in carcinogenicity testing. A number of compounds were tested for carcinogenicity in only one rodent species (Table 2).

Photocarcinogenicity data have been provided for two compounds intended for dermal use (ATC code D11). The studies were performed in addition to conventional long-term rodent carcinogenicity studies using the systemic and dermal route of administration (see Table 1).

Out of the 144 compounds tested for carcinogenicity, 50 (35%) yielded negative results and 94 (65%) were positive in at least one carcinogenicity study or in repeat-dose toxicity studies (Table 3).

Two long-term carcinogenicity studies were available for 116 compounds, 44 of which were negative and 32 of which were positive in both mice and rats. Twenty-two compounds were positive in rats only and 18 were positive exclusively in mice (Table 3).

For 13 compounds, carcinogenicity data were available in only one rodent species. Within this group, three compounds were negative in mice and one compound in rats, while two and seven compounds were positive in mice and rats, respectively (Table 3). One fixed combination product for contraceptive treatment (ATC code G3) yielded positive results in rats, but was shown to be negative in a monkey study of 10-year duration (see Table 1).

Transgenic mouse models were infrequently used as a replacement of a long-term carcinogenicity study. Data from one long-term carcinogenicity study in rats and a transgenic mouse model

Table 2
Categorisation of active substances (INN) with carcinogenicity data according to type and number of studies performed.

Active substances with carcinogenicity data	Number	%
Two long-term carcinogenicity studies	116	81
One long-term carcinogenicity study in rats and one transgenic mouse study	8	5.5
One long-term carcinogenicity study in mice or rats	13	8.5
One transgenic mouse model	1	1
No carcinogenicity studies performed	6	4
Total	144	100

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Table 3
Categorisation of active substances (INN) with carcinogenicity data according to study results.

Active substances with carcinogenicity data	Number	%
All compounds	144	100
- Negative in mice and/or rats	50	35
- Positive in mice and/or rats	94	65
Two long-term carcinogenicity studies	116	80.5
- Negative in mice and rats	44	30.5
- Positive in mice and rats	32	22
- Negative in mice and positive in rats	22	15
- Positive in mice and negative in rats	18	12.5
One long-term carcinogenicity study in rats and one transgenic mouse study	8	
- Negative in mice and rats	2	
- Positive in mice and rats	1	
- Positive in rats and negative in mice	5	
- Negative in rats and positive in mice	0	
One long-term carcinogenicity study in mice or rats	13	
- Negative in mice	3	
- Negative in rats	1	
- Positive in mice	2	
- Positive in rats	7	
One transgenic mouse study	1	
- Negative	1	
- Positive	0	

were available for eight compounds. The TgrasH2 mouse model was used in four studies followed by the p53+/− model which was used twice.

Two compounds showed negative results in the long-term carcinogenicity study in rats and the transgenic mouse study, while five were positive in the long-term rat study and negative in the transgenic mouse study. Only one compound was positive in both the long-term rat study and the transgenic mouse study (Table 3).

For one compound, the only carcinogenicity data available were from a transgenic mouse study, which showed negative results (Table 3).

Of the two compounds tested for photocarcinogenicity in the albino hairless mouse model, one exhibited a negative and one a positive result.

With regard to the rodent species that produced positive carcinogenicity findings, 33 out of 94 compounds were positive in both mice and rats (35%), 40 were positive in rats (43%) and 21 (22%) were positive in mice.

3.2. Overview of genotoxicity data

Out of the 144 compounds with carcinogenicity data, 114 were clearly negative in the standard battery of genotoxicity tests (ICH S2B guideline) or in a more comprehensive test battery. Twelve compounds had positive findings in one or more *in vitro* test(s); however, when considering the results of all genotoxicity tests, the weight of evidence suggested that these compounds had no genotoxic potential. For 18 compounds, the overall results of genotoxicity tests indicated that the compounds may have intrinsic genotoxic properties (Table 4). A more detailed discussion of the compounds with positive or equivocal genotoxicity findings can be found in section 3.3.2.1.

3.3. Individual active substances tested for carcinogenicity

The individual 138 compounds tested for carcinogenicity are shown in Table 1.

In Table 1, active substances (international nonproprietary name, INN) and their reference medicinal products are grouped according to their ATC code and pharmacotherapeutic group. Both the results of genotoxicity and carcinogenicity studies are presented.

In term of genotoxicity, the overall assessment of genotoxicity as stated in the EPAR and/or SPC is presented for each individual compound. However, positive findings in individual genotoxicity studies were also indicated.

With regard to tumour findings in carcinogenicity studies in mice and rats, both benign and malignant neoplasms have been considered in the evaluation. Carcinogenicity studies were assessed as positive if statistically significant increases in tumour incidences were observed. Studies with statistically significant tumour increases that fell within the range of historical control data were classified as positive.

The six compounds exhibiting neoplastic lesions in repeat-dose toxicity studies are shown in Table 5.

3.3.1. Active substances with negative carcinogenicity findings

Out of the 144 compounds with carcinogenicity data, 50 yielded negative results (Table 3). Forty-four compounds were negative in long-term carcinogenicity studies in mice and rats, while two compounds were negative in a long-term study in rats and a transgenic mouse model (Table 3). For four compounds, negative long-term carcinogenicity data were available in only one rodent species (Table 3). One compound was exclusively tested in a transgenic mouse model and was shown to be negative (Table 3). The individual compounds with negative carcinogenicity findings are listed in Table 6.

3.3.2. Active substances with positive carcinogenicity findings

Out of the 144 compounds tested for carcinogenicity, 94 (65%) were positive in at least one carcinogenicity study or in repeat-dose toxicity studies (Table 3).

3.3.2.1. Compounds with positive or equivocal genotoxicity findings. The majority of compounds evaluated for carcinogenicity were found to be devoid of genotoxic properties (Table 4). For 18 compounds, the EPARs concluded that they may have intrinsic genotoxic properties according to the results of the genotoxicity testing battery (Table 7). However, a carcinogenic risk for humans was excluded for those compounds with negative results in long-term rodent carcinogenicity studies and for compounds with rodent-specific tumour findings in carcinogenicity studies (Table 7). The majority of the compounds with positive or equivocal genotoxicity tests and positive long-term rodent carcinogenicity studies are anti-retroviral agents for the treatment of HIV-1 infections and belong to the two classes of anti-retroviral agents

Table 4
Genotoxicity findings for active substances (INN) with carcinogenicity data.

Active substances with carcinogenicity data	Number	%
All compounds	144	100
- Negative in a battery of genotoxicity tests	114	79
- Positive in one or more genotoxicity test(s)	30	21
- Compounds for which the overall results of genotoxicity tests suggested that they have no genotoxic potential	12	10.5
- Compounds for which the overall results of genotoxicity tests suggested that they have intrinsic genotoxic properties	18	12.5

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Table 5
Reference medicinal products for which neoplastic changes were observed in repeat-dose toxicity studies.

Reference medicinal product	ATC code	International nonproprietary name (INN)	Pharmacotherapeutic group	Results of genotoxicity studies	Results of repeat-dose toxicity studies
ATC code A10 Drug used in diabetes					
Novorapid	A10AB05	Insulin aspart	Insulins and analogues for injection, fast-acting	Not genotoxic	Positive in 12-month toxicity study in rats
Protaphane	A10AC01	Insulin human (rDNA)	Insulins and analogues for injection, intermediate-acting, insulin (human)	Not genotoxic	Positive in 12-month toxicity study in rats
ATC code J02 Anti-mycotics for systemic use					
Mycamine	J02AX05	Micafungin	Other antimycotics for systemic use	Not genotoxic	Foci of altered hepatocytes in 6-month toxicity study in rats - developing into tumours during recovery
ATC code J05 Antivirals for systemic use					
Vistide	J05AB12	Cidofovir	Antivirals for systemic use	Genotoxic	Positive in repeat-dose toxicity studies in rats
ATC code L01 Anti-neoplastic agents					
Xagrid	L01XX35	Anagrelide	Other antineoplastic agents	Not genotoxic	Positive in 12-month toxicity study in rats
ATC code V03 All other therapeutic products					
Savene	V03AF02	Dexrazoxane	Detoxifying agents for antineoplastic treatment	Genotoxic	Positive in 12-month toxicity study in mice and rats (NCI study)

NCI: National Cancer Institute.

that are known to be clastogenic, i.e. the nucleoside/nucleotide reverse transcriptase inhibitors and the non-nucleoside reverse transcriptase inhibitors. The carcinogenicity findings observed for these compounds and their potential relevance to humans according to the EPAR and SPC are presented in Table 8.

3.3.2.2. Compounds with rodent-specific or species-specific tumour findings. A high number of tumour findings in rodents were considered to be of no relevance for humans since a species- or rodent-specific mechanism has been identified (Greaves, 2007). These findings are unlikely to pose any carcinogenic risk to humans. Active substances (INN) for which a species- or rodent-specific mechanism was identified in carcinogenicity studies are presented in Table 9.

Liver tumours in mice and rats and thyroid gland follicular cell tumours in rats as a consequence of hepatic microsomal enzyme induction were found most frequently, followed by tumours of the endocrine system including endocrine glands (pituitary gland, adrenal gland), male and female reproductive organs (testes, ovary, uterus) and mammary gland for which rodents are particularly sensitive (Greaves, 2007).

Most of the mechanisms identified were either relevant for both mice and rats, e.g. liver tumours due to hepatic enzyme induction or tumours of endocrine and reproductive system due to disturbances of the hypothalamic–pituitary–gonadal axis, or they were unique to the rat, e.g. thyroid gland follicular cell tumours. Only few tumours were considered to be mouse-specific (Greaves, 2007) (Table 9).

For 38/94 (40%) of the compounds listed in Table 9, tumour findings were exclusively attributable to a rodent-specific mechanism. For these compounds, regulatory actions are not required and wordings indicating that the compounds pose no carcinogenic risk to humans or that the relevance of the tumour findings to humans is minor or limited can be found in the SPC Section 5.3 (for details see Table 10).

3.3.2.3. Compounds with tumour findings due to exaggerated pharmacodynamic effects or secondary to toxic damage. Tumour development related to long-term administration of supraphysiological or toxic doses of compounds is frequently observed in rodent carcinogenicity studies. Active substances (INN) which fall into this category are shown in Table 11. Examples include liver and kidney tumours secondary to hepatic or renal toxicity and lymphomas following administration of immunosuppressive compounds (Greaves, 2007). The mechanisms of carcinogenicity found in rodents are principally also relevant to humans, however, it is unlikely that such tumours will be induced at therapeutic doses.

For many compounds of this group, a sufficiently high safety margin in terms of systemic exposure has been demonstrated in toxicokinetic evaluations (see Section 3.3.2.6). No safety margin has been established for micafungin, tacrolimus, leflunomide, sirolimus, abatacept and amprenavir. The potential relevance of the tumour findings in animals has been included in SPC sections 4.4, 4.8 and/or 5.3 (for details see Table 10).

3.3.2.4. Compounds with photo co-carcinogenic potential. Topical application of tacrolimus (Protopic) shortened the time to skin tumour development induced by UV radiation in albino hairless mice. The underlying mechanism was considered to be systemic immunosuppression based on high exposure levels observed in the animals.

It was included in the SPC Section 5.3 that a risk for humans cannot be completed ruled out as the potential for local immunosuppression with the long-term use of tacrolimus is unknown. A warning to avoid exposure of the skin to sunlight during use of the ointment was included in Section 4.4 of the SPC (see Table 10).

3.3.2.5. Compounds with tumour findings for which the relevance for humans could not be established. This heterogeneous group comprises active substances (INN) with carcinogenicity findings that were either not considered treatment-related or compounds with tumour findings of unknown relevance to humans. An assessment of tumour findings for all compounds with positive carcinogenicity studies and their potential relevance to humans and the corresponding SPC wording is presented in Table 10.

3.3.2.6. Compounds with a high safety margin in terms of systemic exposure. For a considerable number of active substances (INN), systemic exposures in rodents as determined in toxicokinetic assessments were found to be sufficiently in excess of exposure levels at human therapeutic doses (Table 12). Therefore, it was considered that no regulatory actions are required for these medicinal products. Similar statements were included in the SPC Section 5.3 to indicate the large differences in exposure between rodents and humans at therapeutic doses and the low relevance

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Table 6
Active substances (INN) with negative carcinogenicity data.

Active substance
Negative in long-term carcinogenicity studies in mice and rats
Orlistat
Saxagliptin
Nateglinide
Sapropterin
Clopidogrel
Iloprost
Ivabradine
Ambrisentan
Tolvaptan
Irbesartan
Telmisartan
Amlodipine besylate
Valsartan
Nicotinic acid
Eflornithine
Raloxifene hydrochloride
Fesoterodine
Sildenafil
Tadalafil
Vardenafil
Cinacalcet
Saquinavir
Lamivudine
Adefovir dipivoxil
Emtricitabine
Raltegravir
Mycophenolate mofetil
Thalidomide
Ibandronic acid
Alendronate sodium
Levetiracetam
Zonisamide
Lacosamide
Zaleplon
Rivastigmine
Duloxetine
Memantine
Riluzole
Fluticasone furoate
Travoprost
Bimatoprost
Emedastine
Olopatadine
Negative in a long-term carcinogenicity study in rats and a transgenic mouse study
Aliskiren
Deferasirox
Negative in a long-term carcinogenicity study in mice
Imiquimod
Capecitabine
Desloratadine and Pseudoephedrine
Negative in a long-term carcinogenicity study in rats
Levodopa/Carbidopa
Negative in a transgenic mouse study
Capsaicin

of the tumours observed in carcinogenicity studies (for details see Table 10).

3.3.2.7. Product specific assessments of carcinogenic potential. As stated in the ICH S6 guideline, standard rodent carcinogenicity studies are generally inappropriate for biotechnology-derived pharmaceuticals. However, an assessment of the carcinogenic potential may be needed depending on the duration of treatment and the biological activity of the products, e.g. monoclonal antibodies targeting immune functions for the treatment of chronic diseases like rheumatoid arthritis or psoriasis.

When there is a concern about the carcinogenic potential of such products, a variety of approaches may be considered to evaluate the risk. Examples include carcinogenicity testing with a murine analogue of a protein or the treatment of immunocompromised or tumour bearing animals to assess the tumour promoting potential of a product (Table 13).

If no product specific testing is feasible, monitoring of malignancies will be a part of the comprehensive risk management plan of such products.

Table 7
Active substances (INN) with positive or equivocal genotoxicity findings.

Active substance	Carcinogenic potential
Lamivudine Adefovir dipivoxil Mycophenolate mofetil Capecitabine Riluzole Sapropterin	Negative in long-term rodent carcinogenicity studies
Entacapone	Rat-specific mechanism of carcinogenicity identified
Ribavirin Cidofovir Stravudine Abacavir sulphate Tenofovir disoproxil Entecavir Zidovudine Dexrazoxane Rasagiline Hydrochlorothiazide Timolol	Positive in long-term rodent carcinogenicity studies

4. Discussion

Carcinogenicity data of medicinal products for human use that have been authorised via the CP between 1995 and 2009 were evaluated using EPARs and SPCs. In terms of reference medicinal products, carcinogenicity data have been generated for 159 out of 375 centrally authorised products (42%). In terms of active substances (INN), carcinogenicity data, either from long-term rodent carcinogenicity studies, transgenic mouse studies or repeat-dose toxicity studies, were available for 144 individual compounds (see Table 1). Out of the 144 compounds tested for carcinogenicity, 18 (12.5%) exhibited potential genotoxic properties.

With the exception of compounds for which DNA interactions are not expected, e.g. biotechnology-derived pharmaceuticals, genotoxicity studies are routinely required for all medicinal products for human use. Due to the established relationship between exposure to genotoxic compounds and carcinogenesis in man, genotoxicity testing is a fundamental part of carcinogenic risk assessment and compounds with proven genotoxic properties are usually not approvable for human use (ICH S2B guideline). Therefore, it is not surprising that the majority of centrally authorised products with carcinogenicity data exhibited negative genotoxicity findings either in a standard or a more comprehensive test battery. For most of the 18 compounds with potential genotoxic properties, the genotoxic potential was considered to be weak and an exposure threshold with regard to the induction of genotoxic effects appeared to exist. Thus, the relevance of the genotoxic properties to humans was either considered to be low due to a high safety margin in terms of exposure or the clinical benefit was considered to outweigh the potential carcinogenic risk (see Table 8).

Out of the 144 compounds tested for carcinogenicity, 50 (35%) yielded negative results and 94 (65%) were positive in at least one carcinogenicity study or in repeat-dose toxicity studies (Table 2). Based on the negative genotoxicity findings of the majority of compounds, an epigenetic mechanism of carcinogenicity was

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Table 8
Active substances (INN) for which a genotoxic mechanism of carcinogenicity is plausible.

Active substance	Type of tumour	Species	Relevance to humans according to EPAR/SPC
Cidofovir	Mammary adenocarcinoma Zymbal gland carcinoma	Rat	Potential human carcinogen
Stravudine	Liver tumours Urinary bladder carcinoma	Mouse and rat Rat	No relevant risk due to high safety margin
Abacavir sulphate	Tumours of the praeputial and clitoral glands Liver tumours Urinary bladder tumours Lymph node tumours Subcutis haemangiosarcoma	Mouse and rat Rat (f)	Safety margin established Clinical benefit outweighs potential carcinogenic risk
Zidovudine	Vaginal tumours	Mouse and rat	Relevance uncertain, but clinical benefit outweighs potential carcinogenic risk
Entecavir	Lung tumours Vascular tumours Salivary gland tumours (f) Liver tumours (m) Brain tumours (glioma) (m) Pancreas tumours Skin fibroma (f) Zymbal gland carcinoma (f) Liver tumours (f) Uterine haemangiosarcoma (f)	Mouse Rat	Relevance uncertain, but clinical benefit outweighs potential carcinogenic risk
Tenofovir disoproxil	Lipoma (m) Uterus polyps (f) Duodenal tumours Liver adenoma (f)	Rat Mouse	Relevance uncertain, but clinical benefit outweighs potential carcinogenic risk
Dexrazoxane	Haematopoietic neoplasms Uterine adenoarcinoma	Mouse (f) Rat (f)	Known relevance, but clinical benefit outweighs potential carcinogenic risk
Rasagiline	Lung adenoma and carcinomaAQ	Mouse	No relevant risk due to high safety margin
Timolol	Adrenal pheochromocytoma Pulmonary tumours Uterine polyps Mammary gland tumours	Rat (m) Mouse (f)	No relevant risk due to high safety margin

m: Males; f: Females.

Table 9
Active substances (INN) with a species- or rodent-specific mechanism of carcinogenicity.

Active substance	Tumour findings	Species	Mechanism of carcinogenicity*
Pantoprazole Aprepitant Repaglinide Prasugrel Bosentan Voriconazole Ritonavir Fosamprenavir Tipranavir Darunavir Lopinavir/Riponavir Nevirapine Etravirine Eslicarbazepine acetate Stiripentol Agomelatide	Liver adenoma and carcinoma	Rodent	Hepatic microsomal enzyme induction
Pantoprazole Aprepitant Repaglinide Bosentan Voriconazole Indinavir Nelfinavir Fosamprenavir Tipranavir Darunavir Maraviroc Melatonin	Thyroid gland follicular cell adenoma and carcinoma	Rat	Hepatic microsomal enzyme induction Faster clearance of thyroxin and subsequent TSH elevation
Vildagliptin	Mammary gland tumours	Rat	Disturbance of the hypothalamic-pituitary–gonadal axis
Olanazapine Timolol Dronedarone	Mammary gland tumours	Rodent	Disturbance of the hypothalamic-pituitary–gonadal axis Increased prolactin

(*continued on next page*)

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Table 9 (*continued*)

Active substance	Tumour findings	Species	Mechanism of carcinogenicity*
Aripiprazole	Mammary gland tumours Pituitary adenoma	Rodent	
Paliperidone	Mammary gland tumours Pancreas adenoma Pituitary gland adenoma	Rodent	
Norelgestromin/Ethinylestradiol	Mammary gland tumours	Rat	Oestrogenic effect in predisposed strains
Insulin aspart Insulin human (rDNA)	Mammary gland tumours	Rat	Mitogenic and growth promoting action of insulin
Lasofoxifene	Ovarian granulosa cell tumours Uterine polyps Leydig cell tumours Adrenal gland cortical tumours	Rodent	Disturbance of the hypothalamic-pituitary–gonadal axis Increased LH
Fulvestant	Ovarian granulosa cell tumours Leydig cell tumours	Rat	
Sirolimus	Leydig cell adenoma	Rat	
Pramipexole	Leydig cell adenoma	Rat	Disturbance of the hypothalamic-pituitary–gonadal axis Inhibition of prolactin
Rotogotine	Uterus carcinoma Leydig cell adenoma	Rat	
Tolcapone	Uterus carcinoma	Rat	Disturbance of the hypothalamic-pituitary–gonadal axis
Buprenorphine/ Naloxone hydrochloride	Leydig cell adenoma	Rat	
Active substance	Tumour findings	Species	Mechanism of carcinogenicity*
Palonosetron	Pituitary gland tumours Pancreas tumours Mammary gland tumours	Rat	Link between the serotonin and dopamine systems Inhibition of dopamine release
Bazedoxifene	Ovarian granulosa cell tumours	Rodent	Stimulation of ovarian follicle growth Class effect of SERMs
Toremifene	Ovary tumours Testes tumours Osteosarcoma	Mouse	Oestrogenic effect of anti-oestrogens
Posaconazole	Adrenal gland cortical and medullary tumours	Rat	Interruption of steroidogenesis with consequent increased secretion of ACTH, leading to cortical cell proliferation Adrenal medullary tumours as a consequence of altered calcium homeostasis Class effect of azole antifungals
Insulin glargine	Malignant fibrous histiocytoma	Rodent	Injection of solutions with non-neutral pH
Atosiban	Fibroma and fibrosarcoma	Rodent	Injection of irritating materials
Degarelix	Sarcoma	Rodent	
Eptotermin alfa	Sarcoma	Rodent	Implantation of solid material
Teriparatide Parathyroid hormone (rDNA)	Oseosarcoma	Rat	Bone anabolic effect of parathyroid hormone
Rufinamide	Osteoma	Mouse	Activation of a mouse-specific polyomavirus and retrovirus by fluoride ions
Exanatide Liraglutide	Thyroid gland C cell adenoma	Rat	Persistent activation of C cell GLP-1 receptors
Entacapone	Kidney adenoma and carcinoma	Male rat	$\alpha_{2\mu}$ globulin nephropathy
Indacaterol	Mesovarian leiomyoma	Rat	ß adrenergic stimulation
Pregabalin	Haemangiosarcoma	Mouse	Platelet changes and associated endothelial cell proliferation
Brinzolamide	Urinary bladder leiomyosarcoma	Mouse	Histomorphically unique smooth muscle tumour

TSH: Thyroid stimulating hormone.
LH: Luteinizing hormone.
ACTH: Adrenocorticotropic hormone.
SERM: Selctive oestrogen receptor modulator.
GLP-1: Glucagon-like peptide-1.
rDNA: recombinant DNA.
* According to Greaves, 2007.

likely for most of the compounds with positive carcinogenicity findings.

Two long-term rodent carcinogenicity studies were available for 116 compounds (81%), 44 of which were negative and 32 of which were positive in both mice and rats. Twenty-two compounds were positive in rats only and 18 were positive exclusively in mice (see Table 3). Data from one long-term carcinogenicity study in rats and a transgenic mouse model were available for eight compounds (6%). Two compounds showed negative results in one long-term carcinogenicity study in rats and a transgenic mouse study, while five were positive in the long-term rat study and negative in the transgenic mouse study. Only one compound was positive in both the long-term rat study and the transgenic mouse study (see Table 3). For 13 compounds (9%), carcinogenicity data were available in only one rodent species. Within this group, three compounds were negative in mice and one compound in rats,

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Table 10
Overview of active substances (INN) with tumour findings in carcinogenicity and repeat-dose toxicity studies.

Active substance	Tumour findings	Mechanism of carcinogenicity	Relevance for humans according to EPAR/SPC	SPC section 5.3
ATC code A Drugs acting on the gastrointestinal system and on the metabolism				
ATC code A02 Drugs for acid related disorders				
Pantoprazole	Mouse: Liver Rat: Stomach (gastric fundus) Liver Thyroid gland	Rodent-specific Secondary to elevated gastrin Rodent-specific Rodent-specific	Liver and thyroid gland tumours not relevant Stomach tumours not relevant due to high safety margin	Stomach tumours due to chronic high treatment of rats Liver tumours due to high metabolic rate of pantoprazole in the liver Thyroid gland tumours due to breakdown of thyroxine in the liver
ATC code A03Drugs for functional gastrointestinal disorders				
Prucalopride	Mouse: Mammary gland Rat: Liver (adenoma) Thyroid gland (follicular cells) Mammary gland (benign) Pituitary gland Pancreas (islet cells) Adrenal medulla (phaeochromocytoma)	No strong support for a non-genotoxic mechanism from mechanistic studies Genotoxic mechanism cannot be ruled out	Genotoxic mechanism relevant to humans cannot be ruled out	No special hazard for humans
ATC code A04 Anti-emetics and anti-nauseants				
Palonosetron	Rat: Pancreas Pituitary Mammary gland Adrenals Thyroid gland Liver Skin Tail	Mainly tumours of the endocrine system to which rodents are particularly susceptible Stimulation of dopamine release	Not relevant due to high safety margin	Tumour findings not considered relevant since high doses were employed in rats and single administration is to be used in humans
Aprepitant	Rat: Liver Thyroid gland (follicular cells)	Rodent-specific Rat-specific	Not relevant	No special hazard for humans
ATC code A10 Drug used in diabetes				
Insulin glargine	Mouse: Fibrous histiocytoma Rat: Fibrous histiocytoma	Rodent-specific	Not relevant	No special hazard for humans
Insulin aspart	Rat: Mammary gland	Rat-specific	Not relevant	No special hazard for humans
Insulin human (rDNA)	Rat: Mammary gland	Rat-specific	Not relevant	No special hazard for humans
Metformin	Rat: Uterus (benign polyps)	No tumour promoting effect known from the literature	Unlikely to be relevant	No special hazard for humans
Glimepiride	Mouse: Pancreas (islet cells) Lung (adenoma) Rat: Uterus	Chronic pancreatic stimulation Unknown Unknown	Not relevant due to high safety margin	Carcinogenic effects observed only at exposures sufficiently in excess of human exposure or caused by a pharmacodynamic effect
Rosiglitazone	Rat: Adipose tissue (lipoma)	Overstimulation of adipocytes	Relevant in principle No safety margin	Increased colon tumours In an animal model for familial adenomatous polyposis Relevance of this finding is unknown, however, no evidence of colon tumours in lifetime studies in rodents
Pioglitazone	Rat: Urinary bladder	Irritation due to urinary calculi formation	Relevance unknown	Relevance of tumour finding is unknown
Sitagliptin	Rat: Liver	Secondary to hepatic toxicity	Not relevant due to high safety margin	Liver tumours secondary to hepatic toxicity not considered relevant due of high safety margin
Vildagliptin	Mouse: Mammary gland Blood vessels (haemangiosarcoma)	Rodent-specific Promoting effect on tumour commonly observed in mice	Not relevant due to high safety margin	No significant risk due to high safety margin
Repaglinide	Rat: Liver Thyroid gland (follicular cells)	Rodent-specific Rat-specific	Not relevant	No special hazard for humans
Exenatide	Rat: Thyroid gland (C cells) (f)	Rat-specific	Not relevant	Tumours at plasma exposure 130-fold the human clinical exposure Incidence not statistically significant when adjusted for survival
Liraglutide	Mouse: Thyroid gland (C cells) Uterus (leioma/leiosarcoma) Skin (sarcoma)	C cell tumours rodent-specific No dose–response relationship for leioma/leiosarcoma and mice very sensitive to this tumour Skin tumours situated around the microchip No relevant dose related effect for	Thyroid C cell tumours not relevant Uterus leioma/leiosarcoma and skin sarcoma were not considered related Pituitary carcinoma and uterine stromal polyps	Thyroid C cell tumours in mice and rats were caused by a specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive The relevance for humans is likely to be low, but cannot completely ruled out

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Table 10 (*continued*)

Active substance	Tumour findings	Mechanism of carcinogenicity	Relevance for humans according to EPAR/SPC	SPC section 5.3
	Rat:Thyroid gland (C cells) Pituitary gland (f) Uterus (polyps)	pituitary carcinoma and uterine polyps	unlikely to present a risk for humans	
ATC code A16 Other alimentary drugs				
Miglustat	Mouse: Large intestine Rat: Testes (Leydig cells)	Unknown Rat-specific mechanism established	Relevance of large intestine tumours unknown	A safety margin was established The relevance of carcinoma of the large intestine for humans cannot be completely ruled out
ATC code B Blood and blood forming organs				
ATC code B01 Anti-thrombotic agents				
Prasugrel	Mouse: Liver	Rodent-specific	Not relevant	Liver tumours considered secondary to hepatic enzyme induction The increase in liver tumours in mice is not considered a relevant human risk
ATC code C Cardiovascular system				
ATC code C01 Cardiac therapy				
Ranolazine	Rat:Adrenal cortex Adrenal medulla Thyroid gland Testes Skin (sarcoma)	Genotoxic metabolite	Carcinogenic metabolite not found in humans	No relevant increases in the incidence of any tumour types were seen in carcinogenicity studies in mice and rats
ATC code C02 Anti-hypertensives				
Bosentan	Mouse: Liver (m) Rat: Thyroid gland (m)	Rodent-specific Rat-specific	Not relevant	There was evidence for a mild thyroid hormonal imbalance induced in rats, but no evidence of bosentan affecting thyroid function in humans
Sitaxentan sodium	Rat:Adrenal medulla (pheochromcytoma) (m) Skin tumours (m)	Tumours probably not related	Tumours not considered related based on historical control data and statistical analyses	Sixatexan sodium was not carcinogenic
ATC code C09Agents acting on the renin-angiotensin system				
Hydrochlorothiazide	Mouse: Liver (m)	Unknown	Unlikely to be relevant	Extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms
ATC code C10 Lipid modifying agents				
Colesevelam	Rat:Pancreas (islet cells) (m) Thyroid gland (C cells)	Not clinically relevant Slight increase considered incidental since thyroid adenoma are common in old rats	Not relevant due to high safety margin	Carcinogenic effects observed only at exposures sufficiently in excess of maximum human exposure indicating little relevance to clinical use
Laropiprant	Mouse: Testes	Tumours not considered related due to atypical absence of spontaneous tumours in controls	Not related High safety margin	Laropiprant was not carcinogenic
ATC code D Dermatologicals				
ATC code D11 Other dermatological preparations				
Tacrolimus (topical)	Mouse: Lymphoma Hairless mouse photocarcino-genicity: Skin tumours	Systemic immunosuppressive effect	Potential for local immunosuppression unknown	In a dermal carcinogenicity study in mice, lymphoma were observed in association with high systemic exposure In a photocarcinogenicity study in hairless mice, a reduction in time to skin tumour and an in crease in the number of tumours was observed A risk for humans cannot be completely ruled out as the potential for local immuno-suppression with long-term use of tacrolimus ointment is unknown
ATC code G Genito-urinary system and sex hormones				
ATC code G02 Other gynecologicals				
Atosiban	Rat: Injection site (fibroma/fibrosarcoma)	Rodent-specific	Not relevant	Atosiban was not carcinogenic
Norelgestromin/ Ethinyl estradiol	Rat: Mammary gland	Rat-specific	Not relevant	No special hazard for humans
Lasofoxifene	Mouse: Adrenal cortex Ovary (granulose cells) Uterus (polyps) Testes (Leydig cells)Rat: Ovary Kidney (m)	Rodent-specific Male rat specific expression of ERα versus ERß	Not relevant Relevance unknown	Although all of the observed tumours are believed to be the result of rodent-specific hormonal mechanisms, the relevance for humans is currently unknown
Bazedoxifene	TgHras2 mouse model: Ovary (granulosa cells) Rat: Ovary (granulosa cells)	Rodent-specific	Not relevant	Ovary tumours are a class effect of SERMs, related to its pharmacology in rodents when treated during their reproductive lives, when their ovaries are functional and responsive to hormonal stimulation

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Table 10 (*continued*)

Active substance	Tumour findings	Mechanism of carcinogenicity	Relevance for humans according to EPAR/SPC	SPC section 5.3
ATC code G04 Urologicals				
Darifenacin	Rat:Adrenal cortex (f) Blood vessels (haemangiosarcoma) (m)	Tumours not considered related	Tumour not considered related	No special hazard for humans
ATC code H Systemic hormonal preparations, excluding sex hormones and insulins				
ATC code H01 Pituitary and hypothalamic hormones and analogues				
Mecasermin	Rat:Adrenal medulla (phaeochromocytoma) Skin (keratoacanthoma) (m) Mammary gland (m + f)	Promotion of a common spontaneous tumour due to mitogenic/anti-apoptotic effect Indirect effect due to effect on calcium metabolism, blood glucose, body weight and food consumption	Relevance unknown	An increased incidence of pheochromo-cytoma, keratoacanthoma in the skin and mammary gland carcinoma were observed in the rat carcinogenicity study
ATC code H05 Calcium homeostasis				
Teriparatide	Rat: Bone (osteosarcoma)	Rat-specific	Not relevant	Due to the differences in bone physiology in rats and humans, the clinical relevance of bone tumours is probably minor
Parathyroid hormone (rDNA)	Rat: Bone (osteoma/ osteosarcoma)	Rat-specific	Not relevant	Due to the differences in bone physiology in rats and humans, the clinical relevance of bone tumours is probably minor
ATC code J Anti-infectives for systemic use				
ATC code J02 Anti-mycotics for systemic use				
Voriconazole	Mouse: Liver Rat: Liver	Rodent-specific	Not relevant	No special hazard for humans
Posaconazole	Rat:Adrenal cortex Adrenal medulla (pheochromocytoma)	Rat-specific	Not relevant	No special hazard for humans
Micafungin	Rat: Liver	Secondary to hepatotoxicity	Relevant since no safety margin could be established	SPC Sections 4.4 and 5.3: Foci of altered hepatocytes were observed in rat repeat-dose toxicity studies Increased tumour rates were observed at the end of a 12-month recovery period A reliable safety margin could be established The relevance of the tumour finding for the therapeutic use cannot be excluded Liver function should be carefully monitored during treatment Early discontinuation in the presence of elevated AST/ALT is recommended
ATC code J05 Antivirals for systemic use				
Cidofovir	Rat:Mammary gland Zymbal's gland	Genotoxic	Relevant	Tumours were observed in rats at subtherapeutic plasma levels and within3 months of treatment SPC section 4.4: Cidofovir should be considered a potential carcinogen in humans
Ribavirin	Rat: Thyroid gland (C cells) (f)	Increased tumour incidence in females most likely due to increased survival rate	Not relevant	Carcinogenic potential in humans is unlikely
Indinavir	Rat: Thyroid gland	Rat-specific	Not relevant	Tumours probably related to an increase in release of TSH secondary to an increase in thyroxin clearance The relevance of the finding is likely to be limited
Ritonavir	Mouse: Liver (m)	Rodent-specific	Not relevant	Species-specific tumourigenic potential, which is regarded as of no relevance for humans
Nelfinavir	Rat: Thyroid gland	Rat-specific	Not relevant	Treatment of rats with nelfinavir produced effects consistent with enzyme induction, which predisposed rats, but not humans, to thyroid neoplasms The weight of evidence indicates that nelfinavir is unlikely to be a carcinogen in humans
Amprenavir	Mouse: Liver (adenoma) (m) Rat: Liver (adenoma) (m)	Secondary to hepatotoxicity	Relevance unknown	The mechanism for the tumour findings was not elucidated The increased incidence was reported with a low safety margin and the clinical relevance in humans in unknown It should be considered that liver changes were also seen in repeat-dose toxicity studies in rats and dogs The liver can be regarded as a target organ for toxicity
Lopinavir/ Ritonavir	Mouse: Liver	Rodent-specific	Not relevant	Mitogenic induction of liver tumours, generally considered to have little relevance to human risk
Fosamprenavir	Mouse: Liver Rat:Thyroid gland (follicular cells)	Rodent-specific Rat-specific Unknown	Not relevant Relevance unknown	Liver findings are consistent with hepatic enzyme induction, which predisposes rats to thyroid neoplasms

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Table 10 (*continued*)

Active substance	Tumour findings	Mechanism of carcinogenicity	Relevance for humans according to EPAR/SPC	SPC section 5.3
	Uterus			The incidence of uterus tumours was slightly increased over concurrent controls, but was within background range for female rats The relevance of the uterus tumours for humans is uncertain There is no evidence to suggest that the tumour findings are of clinical significance
Atazanavir sulphate	Mouse: Liver (adenoma) (f)	Secondary to hepatotoxicity	Not relevant at therapeutic exposures	Tumours likely to be secondary to cytotoxic liver changes and considered to have no relevance for humans at therapeutic exposures
Tipranavir	Mouse: Liver Rat: Liver Thyroid gland	Rodent-specific Rat-specific	Not relevant	Species-specific tumourigenic potential, which is regarded as of no clinical relevance
Darunavir	Mouse: Liver Rat: Liver Thyroid gland (m)	Rodent-specific Rat-specific	Not relevant	The observed liver and thyroid gland tumours are considered to be of limited relevance to humans
Stravudine	Mouse: Liver Rat: Liver Urinary bladder	Genotoxic	Not relevant due to high safety margin	Tumours were observed at very high exposure levels suggesting an insignificant carcinogenic potential in clinical therapy
Abacavir sulphate	Mouse: Preputial gland Clitoris glandRat: Preputial gland Clitoris gland Thyroid gland (m) Liver (m) Urinary bladder (m) Lymph nodes (m) Subcutis (m)	Genotoxic	Safety margin established Clinical benefit outweighs carcinogenic risk	Systemic exposure at the no effect level was equivalent to 3–7 times the human systemic exposure during therapy While the carcinogenic potential in humans is unknown, these data suggest that a carcinogenic risk is outweighed by the potential clinical benefit
Tenofovir disoproxil	Mouse: Duodenum Liver (adenoma) (f)Rat: Adipose tissue (lipoma) (m) Uterus (polyps)	Genotoxic Duodenal tumours in mice due to formalaldehyde released from tenofovir disoproxil	Tumours in rats not considered related Tumours in mice not considered to present a significant carcinogenic risk for humans	Low incidence of duodenal tumours in mice, considered likely related to high concentrations of tenofovir disoproxil in the gastrointestinal tract Findings unlikely to be relevant to humans
Entecavir	Mouse: Lung Blood vessels (f) Salivary gland (f) Liver (m)Rat: Brain (glioma) Pancreas (acinar cells) (m) Skin (fibroma) (f) Zymbal's gland (f) Uterus	Genotoxic	Key event in lung tumour development species-specific Predictivity of findings for humans is unknown	Lung tumours in mice were preceded by pneumocyte proliferation which was not observed in rats, dogs or monkeys Increased incidences of other tumours were seen only at high life-time exposures, however, the effect levels could not be precisely established Predictivity of the findings for humans is not known
Telbivudine	Rat:Pancreas (acinar cells) Adrenal medulla (phaeochromocytoma) Mammary gland (fibroadenoma)	Size of the effects and lack of dose response suggested that findings are incidental	Not relevant	No special hazard for humans
Nevirapine	Mouse: Liver Rat: Liver	Rodent-specific	Not relevant	Liver tumours are most likely to nevirapine being a strong inducer of liver enzymes
Efavirenz	Mouse: Liver (f) Lung (f)	Unknown	Relevance unknown, but clinical benefit outweighs potential carcinogenic risk	While the carcinogenic potential in humans is unknown, the data suggest that the clinical benefit outweighs the potential carcinogenic risk to humans
Etravirine	Mouse: Liver (f)	Rodent-specific	Not relevant	Liver tumours generally considered to be rodent-specific, associated with liver enzyme induction, and of limited relevance to humans
Oseltamivir	Rat:Blood vessels (haemangioma/haemangiosarcoma) Lymphoid system (m) Epithelia (f)	Typical tumours of rodent strain used	Findings in rats of minor significance	Trend towards a dose-dependent increase in the incidence of some tumours that are typical for the rodent strains used Considering the margin of exposure in relation to the expected exposure in the human use, these findings do not change the risk–benefit in the adopted indications
Zidovudine	Mouse: Vagina Rat: Vagina	Genotoxic	Relevance for humans is uncertain due to metabolic differences between rodents and humans	An intravaginal carcinogenicity study comfirmed that vaginal tumours were the results of long-term exposure of the vaginal epithelium to high concentrations of unmetabolised zidovudine in urine
Maraviroc	Rat:Thyroid gland	Rat-specific	Not relevant	Thyroid tumours in rats were considered of low

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Table 10 (*continued*)

Active substance	Tumour findings	Mechanism of carcinogenicity	Relevance for humans according to EPAR/SPC	SPC section 5.3
	Bile duct (cholangioma/ cholangiosarcoma)	Unknown	Not relevant due to high safety margin	human relevance Bile duct tumours in rats were reported at a systemic exposure at least 15 times the expected human exposure
ATC code L Anti-neoplastic and immunomodulating agents *ATC code L01 Anti-neoplastic agents*				
Gefitinib	Mouse: Liver (adenoma) Rat:Liver (adenoma) Mesenteric lymph nodes (haemangiosarcoma) (f)	Unknown	No safety margin established Relevance unknown	Liver adenoma and mesenteric lymph node haemagiosarcoma were observed in rats Liver adenoma were also observed in mice The clinical relevance of these findings is unknown
Everolimus	Mouse: Leukaemia (granulocytic)	Unknown	No safety margin established, but clinical benefit outweighs potential carcinogenic risk	Carcinogenicity studies in mice and rats did not indicate any tumourigenic potential
Celecoxib	Mouse: Blood vessels (haemangiosarcoma) (f) Pituitary (f)Rat: Liver (m)	Tumour incidences appeared to be with values of historical controls	No safety margin established Clinical benefit outweighs carcinogenic risk	No information presented
Anagrelide	Rat:Adrenal medulla (phaeochromocytoma) Uterus (m)	Exaggerated pharmacological effect Hepatic enzyme induction	Not relevant due to high safety margin	Adrenal medulla and uterus tumours were observed at high exposure levels There is no clinical evidence that the findings are of relevance to human use
ATC code L02 Endocrine therapy				
Toremifene	Mouse:OvaryTestesBone	Mouse-specific	Not relevant	Little relevance for the safety in man, where toremifene acts mainly as an anti-oestrogen
Fulvestrant	Rat:Ovary (granulosa cells) Testes (Leydig cells)	Rat-specific	Not relevant	Induction of tumours is consistent with pharmacology-related endocrine feedback alterations These findings are not of clinical relevance for the treatment of postmenopausal women with advanced breast cancer
Degarelix	Mouse: Liver (adenoma) Lung (adenoma) (f) Injection site (sarcoma)Rat: Lymph nodes (haemangiosarcoma) (f)	Unknown Rodent-specific Not considered related	Unknown Not relevant Probably not relevant due to low incidence and no concurrent increase in males	No special hazard for humans
ATC code L04 Immunosuppressants				
Leflunomide	Mouse: Lymphoma (m) Lung (f)	Immunosuppression Unknown	Relevant Relevance unknown	Malignant lymphoma observed in male mice were considered to be due to the immuno-suppressive activity The relevance of the lung tumours in female mice is uncertain. SPC section 4.8: The risk of lymphoproliferative disorders is increased with use of some immuno-suppressive agents
Sirolimus	Mouse: Lymphoma Leukaemia (f) Liver (m) Rat: Testes (Leydig cells)	Immunosuppression Rat-specific	Relevant Not relevant	Lymphoma secondary to chronic use of immunosuppressive agent can occur and have been reported in patients in rare instances Testes tumours were considered to be due to a species-specific response to LH levels and of limited clinical relevance
Abatacept	Mouse: Lymphoma Mammary gland (f)	Decreased control of viral infections due to immunosuppression	Relevant	Malignant lymphoma and mammary tumours in mice may be associated with decreased control of murine leukaemia virus and mouse mammary tumour virus, respectively, in the presence of long-term immunomodulation The relevance of these findings to the clinical use of abatacept is unknown SPC section 4.4 and 4.8: Immunosuppression increases the susceptibility to the development of lymphoma and other malignancies
Tacrolimus (systemic)	Mouse (topical application): Lymphoma	Systemic immunosuppressive effect	Relevant	In mice, topical administration of tacrolimus was associated with high systemic exposure levels resulting in the formation of lymphoma SPC section 4.4 and 4.8: Increased risk of malignancies secondary to immunosuppression
ATC code M Musculo-skeletal system *ATC code M05 Drugs for treatment of bone diseases*				

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Table 10 (*continued*)

Active substance	Tumour findings	Mechanism of carcinogenicity	Relevance for humans according to EPAR/SPC	SPC section 5.3
Zoledronic acid	Mouse: Harderian gland	Unknown	Tumour findings not considered relevant	Carcinogenicity studies did not provide any evidence of a carcinogenic potential
Eptotermin alfa	Rat: Implantation site (sarcoma)	Rodent-specific	Not relevant	Sarcoma in rats was associated with the long-term presence of heterotopic bone Solid state carcinogenicity is frequently observed in rats when solid materials are implanted subcutaneously There is evidence to suggest that heterotopic ossification is not linked to sarcoma in humans
Strontium ranelate	Rat: Thyroid gland (C cells) (m)	Incidences within historical control range	Not related	No special hazard for humans
ATC code N Nervous system				
ATC code N03 Anti-epileptics				
Rufinamide	Mouse: Bone (osteoma) Liver	Activation of a mouse-specific virus by fluoride ions	Not relevant	Osteomas were considered a result of activation of a mouse-specific virus by fluoride ion released during oxidative metabolism of rufinamide
Eslicarbazepine acetate	Mouse: Liver	Rodent-specific	Not relevant	Liver tumours consistent with an induction of hepatic microsomal enzymes
Pregabalin	Mouse: Blood vessels (haemangioma)	Mouse-specific	Not relevant	Platelet changes and associated endothelial proliferation were not present in rats or humans No evidence to suggest an associated risk to humans
Stiripentol	Mouse: Liver	Rodent-specific	Not relevant	Special susceptibility of the mouse liver to tumour formation in the presence of hepatic enzyme induction Liver tumours were not considered to indicate a risk of tumourigenicity in humans
ATC code N04 Anti-Parkinson drugs				
Pramipexole	Rat: Testes (Leydig cells)	Rat-speciific	Not relevant	Tumours can be explained by a prolactin-inhibiting effect of pramipexole The finding is not clinically relevant to man
Rotogotine	Rat:Testes (Leydig cells) Uterus	Rat-specific	Not relevant	Tumours are well-known effects of dopamine-agonists in rats and assessed as not relevant to man
Rasagiline	Mouse: Lung	Genotoxic	Not relevant due to high safety margin	Lung tumours were observed in mice at systemic exposures 144–213 times the expected plasma exposure in humans
Tolcapone	Rat:Kidney Uterus	Secondary to nephrotoxicity Species-specific	Safety factor was established Not relevant	Renal epithelial tumours were observed in the mid- and high-dose groups in rats, however, there was no evidence of renal toxicity in the low-dose group Uterine adenocarcinoma were observed in the high-dose group in rats
Entacapone	Rat: Kidney (m)	Male rat-specific	Not relevant	No special hazard for humans
ATC code N05 Psycholeptics				
Olanzapine	Mouse: Mammary gland (f) Rat: Mammary gland (f)	Rodent-specific	Not relevant	Based on the results of carcinogenicity studies in mice and rats, it was concluded that olanzapine is not carcinogenic
Aripiprazole	Mouse: Mammary gland (f) Pituitary gland (f)Rat: Mammary gland (f) Adrenal cortex (f)	Rodent-specific Cytotoxicity due to increased oxidative stress	Mammary and pituitary tumours not relevant Safety margin established for adrenocortical tumours	Carcinogenic effects observed at doses/exposures sufficiently in excess of the maximum human dose/exposure, indicating that these effects were of limited or no relevance to clinical use
Paliperidone	Mouse: Mammary gland (f) Pituitary gland (f)Rat: Mammary gland (m + f) Pancreas (islet cells) (m)	Rodent-specific	Not relevant	The observed tumours of the pituitary gland, endocrine pancreas and mammary gland can be related to prolonged dopamine antagonism and hyperprolactinaemia The relevance of these tumours in terms of human risk is unknown
Melatonin	Rat:Pituitary gland (m) Thyroid gland (follicular cells)	Pituitary tumours common in rats Statistical significance of pituitary tumours below the value of triggering concern Thyroid tumours rat-specific	Not relevant	The carcinogenicity study in rats did not reveal any effect which may be relevant for humans
ATC code N06 Psychoanaleptics				
Agomelatine	Mouse: Liver Rat:Liver (m) Mammary gland (fibroadenoma) (m + f)	Liver tumours rodent-specific Mammary gland tumours unknown	Not relevant due to high safety margins	Liver tumours were most likely related to enzyme induction specific to rodents The frequency of mammary fibroadenoma in rats was increased with high exposures
ATC code N07 Other nervous system drugs				
Varenicline	Rat: Brown fat	Increased sympathetic	In humans, brown fat is	There was a dose-related increase in the

Table 10 (*continued*)

Active substance	Tumour findings	Mechanism of carcinogenicity	Relevance for humans according to EPAR/SPC	SPC section 5.3
tartrate	(hibernoma)	stimulation of brown adipocytes	present at birth, after which its metabolic activity and thermogenic capacity decreases to minimal levels. Therefore, the risk for humans is theoretical and probably non-existent	incidence of hibernoma in male rats
Buprenorphine hydrochloride/naloxone hydrochloride	Rat: Testes (Leydig cells)		Rat-specific	Not relevant
Statistically significant increases in the incidence of Leydig cell adenoma were observed in rats at all dose groups at exposure multiples of 3–75 times				
Sodium oxybate	Mouse (γ-butyrolactone): Adrenal medulla (pheochromocytoma) (f) Rat (sodium oxybate): Pituitary gland (f)	Tumours slightly increased and difficult to interpret due to high mortality Doubtful statistical significance and incidence was at the upper bound of historical controls	Unlikely relevant	In a mouse study with γ-butyrolactone, results were equivocal due to a slight increase of pheochromocytoma, which was difficult to interpret due to high mortality In a rat study with sodium oxybate, no compound-related tumours were observed
ATC code S Sensory organs				
ATC code S01 Ophthalmologicals				
Brinzolamide	Mouse: Urinary bladder (leiomyosarcoma) (f)	Mouse-specific	Not relevant	Smooth muscle tumour was considered unique to mice
Timolol	Mouse: Lung (f) Uterus (benign polyps) Mammary glandRat: Adrenal medulla (pheochromcytoma)	Unknown UnknownRodent-specific Unknown	Not relevant due to high safety margin	No special hazard for humans
ATC code V Various				
ATC code V03 All other therapeutic products				
Sevelamer (carbonate)	Mouse: Lymphoma Rat: Urinary tract and bladder (m)	Not considered related to treatment Due to crystalline deposits in the urine	Tumours not considered related Relevance unknown	In rats, there was an increased incidence of urinary bladder transitional cell papilloma in males of the high-dose group
Dexrazoxane	Mouse: Haematopoietic tumours (f) Rat: Uerus	Clastogenic	Probably relevant	Secondary malignancies in mice and rats after prolonged administration
Not yet classified				
Dronedarone	Mouse: Haemolymphoreticular system (sarcoma) Mammary gland (f) Harderian gland (f)Rat: Mesenteric lymph nodes (haemangioma)	Mammary tumours rodent-specific Haemangiosarcoma unknown	Not relevant due high safety margin	None of the tumour findings were considered relevant for humans
Indacaterol	Rat: Ovary (leiomyoma)	Rat-specific	Incidence of tumour not increased in women following use of adrenergic agents	Similar findings in rats reported for other $ß_2$ agonists Safety margin in terms of exposure

m: Males; f: Females.
ER: Oestrogen receptor.
AST: Aspartate aminotransferase.
ALT: Alanine aminotransferase.
TSH: Thyroid stimulating hormone.
LH: Luteinizing hormone.

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Table 11
Active substances (INN) with carcinogenic effects attributable to exaggerated pharmacodynamic effects or toxic damage.

Active substance	Tumour findings	Species	Mechanism of carcinogenicity*
Pantoprazole	Stomach squamous papilloma and carcinoma	Rat	Secondary to massively elevated serum gastrin levels
Glimepiride	Pancreatic islet cell adenoma	Rat	Chronic islet cell stimulation
Sitagliptin	Liver tumours	Rat	Secondary to hepatotoxicity
Atazanavir sulphate			
Amprenavir		Mouse	
Micafungin		Mouse and rat	
		Rat	
Tolcapone	Renal epithelial tumours	Rat	Secondary to nephrotoxicity
Tacrolimus	Lymphoma	Mouse	Due to immunosuppressive action
Leflunomide			
Sirolimus			
Abatacept			
Pioglitazone	Urinary bladder transitional cell tumours	Male rat	Irritation due to urinary calculi formation
Sevelamer			

* According to Greaves, 2007.

while two and seven compounds were positive in mice and rats, respectively (see Table 3). For one compound, the only carcinogenicity data available were from a transgenic mouse study, which showed negative results (see Table 3). Six compounds (4%) were tumourigenic in repeat-dose toxicity studies in rats (see Table 5). Out of the 94 compounds with positive findings in either carcinogenicity or repeat-dose toxicity studies, 33 compounds were positive in both mice and rats (35%), 40 were positive in rats only (43%) and 21 were positive in mice only (22%). Thus, the majority of positive carcinogenicity findings (78%) have been produced in rats.

A similar analysis of carcinogenicity data all pharmaceuticals (NCEs) that were submitted to the regulatory authorities from Germany and The Netherlands between 1980 and 1995 (including those which were withdrawn or not approved later on) was performed by Van Ousterhout et al. (1997). The analysis showed that 181 out of 221 compounds (approximately 82%) were tested in two rodent long-term carcinogenicity studies and 40 compounds (18%) were tested in either mice or rats (or the second species was replaced, e.g. by hamsters). When comparing the two evaluations, it is of note that the frequency of using two long-term carcinogenicity studies has not changed during the last 15 years and the acceptance of transgenic mouse models as a replacement of the second long-term study is considered to be poor.

In terms of positive tumour findings, Van Ousterhout et al. found that 106 out of 221 compounds (48%) were positive in at least one long-term carcinogenicity study. Approximately 44% positive pharmaceuticals were found in an evaluation of carcinogenicity studies in the FDA database and NTP rodent carcinogenicity database (Contrera et al., 1997).

Considerably more compounds with positive tumour findings, i.e. 94/144 (65%) were identified in the evaluation of the EPARs, although the classification of tumours was similar to that used by Van Ousterhout et al. A particular reason for the higher number of positive findings could not be determined.

In the evaluation by Van Ousterhout et al., 92 out the 106 compounds with positive carcinogenicity findings were positive in both mice and rats (34) or in rats only (58). Thus, approximately 87% of the compounds showed positive results in rats and only 13% were positive in mice, but not in rats. In the evaluation of the EPARs, the proportion of compounds that yielded positive results in rats was 78% (21/94). The results are consistent with the view that the rat is more sensitive towards carcinogenic effects than the mouse (Smith, 1996; Van Ousterhout et al., 1997).

As summarised in Table 10, most of the tumour findings observed in carcinogenicity studies in mice and/or rats were considered not to be relevant for humans. Among these were tumour findings for 38 compounds (40%) which were classified as species- or rodent-specific (see Table 9). For all of these tumours, the plausibility of a species- or rodent-specific mechanism of carcinogenicity has been demonstrated by additional mechanistic evaluations including hormone measurements.

For 20 compounds (21%), high safety margins in terms of exposure between the NOAEL in rodents and the recommended therapeutic exposures in humans were established (see Table 12). This indicates the particular importance of toxicokinetic measurement with regard to carcinogenic risk assessment. The systemic exposures determined in rodents were at least five times and up to several thousand times higher than the clinical exposures achieved at maximum therapeutic doses. For most of these compounds, tumour findings in rodent carcinogenicity study were considered not to be relevant for the clinical situation due to demonstrated high exposure differences between rodents and humans (see Table 10 for SPC wordings). However, for certain compounds, e.g. the potentially clastogenic compound abacavir sulphate, a lower safety margin was considered to be acceptable based on the overall risk–benefit evaluation for the medicinal product (see Table 10 for SPC wording for abacavir sulphate).

For 11 compounds (11%), tumours observed in rodent carcinogenicity studies were either considered not related to treatment or were thought not to be relevant for humans. A number of tumours were considered incidental because they fell within the range of historical control data, due to a small effect size and lack of dose–response relationship or due to the fact that the tumours were typically observed in the rodents strains used. Some tumours were considered not relevant for humans based on available literature and clinical data that did not indicate a carcinogenic risk for humans, or based on likely differences in metabolism/concentrations between rodents and humans (for details see Table 10).

Tumours observed for 14 compounds (15%) were considered to be of unknown relevance for humans. For many of the compounds, tumour findings were described in the SPC Section 5.3 and it was stated that the relevance for humans is unknown. However, none of the findings triggered any further regulatory actions (see Table 10).

A potential carcinogenic risk for humans was established for eleven compounds (11%). These compounds have nevertheless been approved for clinical use based on a positive risk benefit assessment. Based on carcinogenic effects observed in repeat-dose toxicity studies in rats, the anti-retroviral agent cidofovir was labelled as a potential human carcinogen in the SPC section 4.4. The immunosuppressive compounds leflunomide, sirolimus, abatacept and tacrolimus[2] caused lymphoma in mouse carcinogenicity studies which are thought to be virus-related. It is well-

[2] Tacrolimus was counted twice as it is approved as topical product for the treatment of atopic dermatitis (ATC code D 11) and systemic treatment of transplant rejection (ATC code L04).

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Table 12
Active substances (INN) with a high safety margin in terms of systemic exposure.

Active substance	Potential mechanism of carcinogenicity
Stravudine Abacavir sulphate Rasagiline Timolol	Genotoxicity
Pantoprazole Glimepiride Sitagliptin Atazanavir sulphate Tolcapone Anagrelide	Exaggerated pharmacodynamic effect or toxic damage
Palonosetron Maroviroc Dronedarone Agomelatine Colesevelam Laropiprant Miglustat Darifenacin Vildagliptin Aripiprazole	Unknown

Table 13
Biotechnology-derived products tested for carcinogenicity.

Reference medicinal product	International nonproprietary name (INN)	Results of mechanistic studies
NeoRecormon	Epoetin beta	Negative in a long-term mouse study with murine epoetin Negative in a rat study with implanted tumours and cyclophosphamide treatment
Remicade	Infliximab	Negative in a repeat-dose toxicity study with anti-mouse TNFα

documented that immunosuppressive agent can cause the development of virus-induced malignancies. Corresponding wordings were included in SPC section 4.4 and 4.8 for these compounds (see Table 10). The antifungal agent micafungin induced liver tumours in rats at exposure levels similar to those seen in humans. The carcinogenic effects of dexrazoxane in rodents were related to its clastogenic activity (see Table 10). For the tumours observed in rodent carcinogenicity studies with the anti-retroviral compound efavirenz and the anti-neoplastic compounds everolimus and celecoxib, the EPAR/SPC indicated that a potential carcinogenic risk is outweighed by their clinical benefit (see Table 10).

Trans-species carcinogenicity findings which are usually considered to pose a relatively greater risk to humans (Contrera et al., 1997) were rarely noted. Trans-species findings included vaginal tumours observed in carcinogenicity studies with zidovidine and liver adenoma observed in carcinogenicity studies with gefitinib. Vaginal tumours were attributed to high concentrations of unmetabolised zidovidine in the urine. The relevance to humans was however considered to be uncertain due to metabolic differences between rodents and humans. The relevance of liver adenoma caused by gefitinib for humans was unknown and a corresponding statement was included in the SPC section 5.3.

In summary, the present evaluation indicated that a high number of compounds contained in centrally approved medicinal products produced positive tumour findings in rodent carcinogenicity studies (94/144, 65%). The majority of the rodent carcinogenicity findings were considered not to be of relevance for humans (69/94, 73%). Genotoxicity, toxicokinetic and mechanistic studies provided important information with respect to the interpretation of rodent tumours findings and their potential relevance for humans.

The necessity for routinely conducting two long-term rodent carcinogenicity studies has been under discussion for many years. The relative individual contribution of mouse and rat carcinogenicity studies and whether the use of rats alone would result in a significant loss of information on carcinogenicity relevant to human risk assessment has been addressed by a number of surveys of data for human pharmaceuticals (ICH S1B guideline; Smith, 1996; Van Ousterhout et al., 1997; Contrera et al., 1997). The analyses led to the recommendation by ICH of conducting one long-term carcinogenicity study in rats which should be supplemented by a transgenic mouse assay or the neonatal rodent tumourigenicity model (ICH S1B guideline).

However, the present evaluation indicated that this approach has basically failed since the carcinogenic potential of the majority of compounds were still evaluated using two long-term carcinogenicity studies (see Table 1).

The evaluation of the EPARs confirmed that the rat was more sensitive than the mouse towards carcinogenic effects with the majority of compounds being positive in both mice and rats or rats alone (73/94, 78%). Although 21 compounds produced carcinogenic effects in mice only, most of the findings were considered not to be relevant for humans and consequently did not trigger any regulatory actions. For the development of lymphoma under treatment with immunosuppressive agents, the mouse was shown to be more sensitive than the rat. However, this is a well-documented phenomenon and considered to be virus-related (see Table 10).

5. Conclusions

The evaluation of carcinogenicity data of centrally authorised medicinal products revealed that for the majority of products two long-term rodent carcinogenicity studies were used for assessment of carcinogenic potential and that the acceptance of transgenic mouse models was low.

The evaluation showed that the majority (69/94, 73%) of positive carcinogenicity findings in rodents were considered not to be relevant for humans. The findings confirmed the results of previous similar reviews of carcinogenicity studies (Monro, 1996; Van Ousterhout et al., 1997).

It can be concluded from the current evaluation that tumour findings in rodents were largely not predictive for human use, particularly for compounds with hepatic enzyme inducing and compounds inducing hormonal disturbances. In addition, carcinogenicity studies were redundant for compounds with immunosuppressive properties due to their known carcinogenic potential in humans. This is consistent with findings from previous reviews (Monro, 1996).

Furthermore, the current analysis revealed that positive carcinogenicity findings in either mice or rats did not trigger any regulatory actions if there was no supportive evidence of their potential relevance for humans from genotoxicity, toxicokinetic or mechanistic studies.

In the current evaluation, a potential relevance for the human situation was established for only 11 compounds (11%) with positive carcinogenicity findings. These compounds were authorised based on a positive risk benefit assessment. It is of note that four of these compounds produced tumour findings in repeat-dose toxicity studies in rats (see Table 5). Four compounds were subjected to carcinogenicity testing despite their immunosuppressive properties which are known to allow the development of virus-related malignancies in both mice and humans (see Table 10).

The lack of accuracy of long-term rodent carcinogenicity studies for predicting human cancer risk has been criticised in the past

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(Monro, 1996; Ennever and Lave, 2003). The current evaluation of the EPARs confirmed the poor predictivity of long-term rodent carcinogenicity studies for the human situation. Therefore, a revision of the current carcinogenicity testing strategy for pharmaceuticals is warranted.

As suggested by previous reviews of carcinogenicity studies (Alden et al., 1996; Van Ousterhout et al., 1997) and by the ICH S1B guideline, long-term carcinogenicity studies in the mouse are unlikely to add any significant value and should not be requested in the future. As suggested by the ICH S1B guideline, the long-term mouse study may be replaced by a transgenic mouse model. The acceptability of this strategy may be improved by a closer collaboration between regulatory agencies and pharmaceutical companies.

A recent compilation of rat chronic toxicity and 2-year carcinogenicity study data of both marketed and non-marketed compounds from a collaboration of 13 pharmaceutical companies demonstrated that rat chronic toxicity studies are good predictors of the negative outcome in long-term rat carcinogenicity studies provided that genotoxicity studies are negative and no preneoplastic changes or hormonal disturbances were observed in chronic rat studies. The evaluation of chronic rat toxicity studies has the potential to eliminate approximately 40% of the long-term rat carcinogenicity studies based on their predictivity for a negative outcome for rat tumour development (Reddy et al., 2010; Sistare, 2010).

Two-year rodent carcinogenicity studies are currently the most expensive and time-consuming animal tests required for pharmaceutical carcinogenicity assessment. Since these studies are largely not predictive of human cancer risk, both pharmaceutical companies and regulatory agencies should aim at their replacement. The collaborative assessment of existing carcinogenicity data from pharmaceutical companies utilising new approaches to identify potentially human relevant or irrelevant mechanisms of carcinogenicity including genetically modified animal models and *in vitro* carcinogenicity screening assays based on gene expression profiling (Vinken et al., 2008; Bercu et al., 2010) are likely to improve the current carcinogenicity testing paradigm without the need of long-term rodent carcinogenicity studies.

Conflict of interest

The authors confirm that they have no conflicts of interests that could inappropriately influence, or be perceived to influence, their work.

Guidelines

ICH S1A: The need for carcinogenicity studies of pharmaceuticals. CPMP/ICH/140/95, July 1996.
ICH S1B: Carcinogenicity: testing for carcinogenicity of pharmaceuticals. CPMP/ICH/299/95, March 1998.
ICH S2B: Genotoxicity: A standard battery for genotoxicity testing of pharmaceuticals. CPMP/ICH/174/95.
ICH S3A: Toxicokinetics: A Guidance for Assessing Systemic Exposure in Toxicology Studies CPMP/ICH/384/95, June 1995.
ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. CPMP/ICH/302/95, March 1998.
ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals. EMEA/CHMP/ICH/646107/2008, November 2009.
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