C/2025/1150

20.2.2025

COMMUNICATION FROM THE COMMISSION

Indicative list of hazardous medicinal products according to Article 18a of Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work

(C/2025/1150)

1. INTRODUCTION

1.1. Hazardous medicinal products (HMPs) and legal context of the project

Hazardous medicinal products (HMPs) include, amongst others, some antineoplastics, immunosuppressants and antiviral medicines and are used to treat a wide range of medical conditions including cancer and rheumatology. HMPs can cause unintended effects in people other than the patients themselves, such as the workers who are exposed to them at the workplace.

The Carcinogens, Mutagens and Reprotoxic Substances Directive 2004/37/EC ([1]) (CMRD) is the main EU legislative tool to ensure workers' protection against risks arising from the exposure to carcinogens, mutagens and reprotoxic substances at the place of work and HMPs, due to their effect mechanism on the body, often fall under these categories.

The European Parliament, the Council and relevant stakeholders support the Commission's commitment to continuously update the CMRD and as part of its fourth amendment ([2]), the Commission was invited by the co-legislators, in article 18a, to establish a definition and indicative list of HMPs: 'Where appropriate and no later than 5 April 2025, taking into account the latest developments in scientific knowledge and after appropriate consultation of relevant stakeholders, the Commission shall develop a definition and establish an indicative list of hazardous medicinal products or the substances contained therein, which meet the criteria for classification as a category 1A or 1B carcinogen set out in Annex I to Regulation (EC) No 1272/2008, a mutagen or a reprotoxic substance.'

1.2. Benefits of an indicative HMPs list

It has to be noted, that the main purpose of this list is to further improve the safety of workers due to exposure to HMPs and not to replace HMPs with medicines that are not hazardous or are less hazardous to workers' health. Indeed, this is rarely an option because the intrinsic properties of the HMPs are usually essential for the patient's treatment and their health should not be compromised.

The more detailed information about HMPs provided by this document aims at improving the quality of the risk assessment according to Directive 89/391/EEC ([3]) and CMRD, thus helping protecting workers in a better way. It has to be noted, that this list cannot replace the mandatory chemical risk assessment of the specific workplace which might take into account other available information such as the concentration of a specific substance or of several substances within the medicinal products. Therefore, the document can only be seen as an indicative, non-binding and complementary element to the above-mentioned risk assessment.

At the same time the indicative list complements the technical information of the Guidance ([4]) published by the Commission in April 2023 and can be seen as another element of awareness raising about the risks linked to working with HMPs.

Furthermore, the indicative HMPs list presents an approach at EU level which does not yet exist and thus helps promoting a more aligned approach between Member States.

([1]) Directive 2004/37/EC of the European Parliament and of the Council on the protection of workers from the risks related to exposure to carcinogens, mutagens, or reprotoxic substances at work (OJ L 158, 30.4.2004, p. 50).

([2]) Directive 2022/431 of the European Parliament and of the Council of 9 March 2022 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (OJ L 88, 16.3.2022, p. 1).

([3]) Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work (OJ L 183, 29.6.1989, p. 1).

([4]) Guidance for the safe management of hazardous medicinal products at work, 2023.

1.3. **Existing hazardous medicinal products lists and systems**

Other than the list presented in this document, the employer can consult the sources presented in Table 2-1 of the Guidance ([5]) showing different lists and information systems established by several countries.

At international level, additional information can be found in the 2020 list proposed by the National Institute for Occupational Safety and Health (NIOSH ([6])) and in the list prepared by the European Trade Union Institute in 2022 ([7]) whose basis is the abovementioned list.

The NIOSH ([8]) list creates no legal obligation for employers; it is advisory in nature and informational in content. The methodology used by NIOSH to evaluate chemical properties, pre-clinical information, and clinical information about each drug has made it a recognised source of information in expert circles.

2. **DEFINITION OF HMPs**

For the purposes of this document, hazardous medicinal products ([9]) are defined ([10]) as medicinal products that contain one or more substances that meet the criteria for classification as:

— Carcinogenic (category 1A or 1B)

— Mutagenic (category 1A or 1B) or

— Toxic for reproduction (category 1A or 1B)

in accordance with Regulation (EC) No 1272/2008 (CLP Regulation) ([11]).

In addition, medicinal products are defined as follows in accordance with Directive 2001/83/EC ([12]):

'*Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or*

Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or

to making a medical diagnosis.'

3. **METHODOLOGICAL APPROACH FOR THE ESTABLISHMENT OF AN INDICATIVE HMPs LIST**

3.1. **Drafting Group and involvement of relevant stakeholders**

The process of developing this document was supported by a Drafting Group including representatives from governments, employers and workers interest groups of the tripartite Advisory Committee for Safety and Health at Work (ACSH) Working Party on Chemicals (WPC). The Drafting Group was led by representatives of the Directorate-General for

([5]) Guidance for the safe management of hazardous medicinal products at work, 2023.

([6]) US Department of Health and Human Services Centers for Disease Control and Prevention National Institute for Occupational Safety and Health: NIOSH List of Hazardous Drugs in Healthcare Settings, 2020.

([7]) European Trade Union Institute's (ETUI's) list of hazardous medicinal products (HMPs) including cytotoxics and based on the EU CLP classification system of Carcinogenic, Mutagenic and Reprotoxic (CMR) substances (2022) is available at: https://www.etui.org/publications/etuis-list-hazardous-medicinal-products-hmps.

([8]) The NIOSH List of Hazardous Drugs in Healthcare Settings assists employers in providing safe and healthy workplaces by identifying drugs approved by the U.S. Food and Drug Administration's Center for Drug Evaluation and Research (CDER) that have intrinsic properties that meet the NIOSH definition of a hazardous drug.

([9]) As the same HMPs are used for both humans and animals (although less common in the animal health sector), the HMPs covered by the above definition also include those used in the veterinary sector.

([10]) Recital 11 of Directive (EU) 2022/431 of the European Parliament and of the Council of 9 March 2022 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (OJ L 88, 16.3.2022, p. 1).

([11]) Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures (OJ L 353, 31.12.2008, p. 1).

([12]) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

Employment, Social Affairs and Inclusion and was also composed of experts from the European Medicines Agency (EMA) and the European Chemicals Agency (ECHA).

The document was endorsed by the WPC and the ACSH.

3.2. **Establishment of an indicative HMPs list**

Following the definition of HMPs mentioned above, the Drafting Group has decided to establish the indicative HMPs list by crossing the information from existing databases of two European Agencies ([13]):

— the ECHA database on hazardous substances

— the EMA database on medicinal products

3.2.1. ***ECHA database on hazardous substances***

The data provided by ECHA for this document originated from the information sources presented below.

3.2.1.1. *Harmonised classification information*

The available information on harmonised classifications for hazardous substances originated from the Annex VI of CLP and of the Registry of Intentions (RoI).

Annex VI of CLP

The official and legally binding harmonised classification and labelling of hazardous substances, including Carcinogenic, Mutagenic and Reprotoxic (CMR) substances, is available from Part 3 of Annex VI to CLP which is regularly updated by the subsequent delegated acts ([14]) published in the *Official Journal of the European Union*.

Registry of classification and labelling intentions until outcome (RoI)

The RoI lists the intentions and proposals received by ECHA for a new or revised harmonised classification and labelling of a substance. It informs on the progress of a proposal from the notification of the intention to the adoption of the opinion of the Committee for Risk Assessment (RAC). It therefore lists, amongst others, substances which are not yet listed in Annex VI of CLP.

3.2.1.2. *Self-classification information*

Under the CLP regulation, manufacturers, importers and downstream users have the obligation to review whether a substance must be self-classified (and notified), if it presents hazardous properties, and has no harmonised classification (Annex VI to CLP) ([15]). To decide on a self-classification, the manufacturer, importer or downstream user must gather all the available information, assess its adequacy and reliability and evaluate it against the classification criteria.

All relevant hazard classes (such as carcinogen, mutagen or toxic to reproduction) must be assessed by the manufacturer, importer or downstream user and a self-classification must be applied to all hazard classes for which the classification criteria are fulfilled. Furthermore, all the hazard classes that are not covered by an entry in Annex VI to CLP must be assessed for self-classification.

([13]) The evaluation of the databases was finished in June 2024.

([14]) Following the adoption of the opinion on the harmonised classification and labelling of a substance by the Committee for Risk Assessment (RAC) of ECHA, the European Commission takes a decision and updates the list of harmonised classifications in Annex VI of CLP on a yearly basis by delegated acts.

([15]) If the substance has a harmonised classification, manufacturers, importers and downstream users have an obligation to classify the substance in accordance with that harmonised classification for hazard classes covered by it.

Self-classifications are submitted to ECHA, either via a REACH registration ([16]) or a classification and labelling (C&L) notification ([17]) (both types can be found in the C&L inventory ([18])). It must furthermore be noted that:

— self-classifications submitted to ECHA, either via REACH registration or C&L notification, may vary between the different parties submitting the notifications.

  This results from the absence of obligation on the EU actors to find an agreement amongst themselves concerning the self-classification:

  — a self-classification submitted to ECHA, via REACH registration, is generally supported by a dossier containing data and prepared by registrants;

  — a self-classification submitted to ECHA, via C&L notification, is not generally supported by a REACH registration dossier ([19]);

— the quality and reliability of the data used for self-classification is generally not assessed by ECHA.

For the purpose of this list, the available information on substances' CMR properties given through self-classifications originated from either a REACH registration or from the C&L inventory notifications.

As per the above, the reliability of data linked to self-classifications is considered to vary compared to that of harmonised classification. In case of uncertainty, with regard to the self-classification of a particular substance, it is recommended that the employer contacts the company in charge of the release of the given HMP on the market to obtain additional information (Material Safety Data Sheet or similar document) concerning the classification of the substance.

3.2.2. *EMA database on medicinal products*

EMA publishes in its Article 57 ([20]) database information on all medicines authorised in the EU and European Economic Area (EEA). Marketing authorisation holders must submit and maintain this information in accordance with the European Union legislation.

3.2.3. *Linking of ECHA and EMA databases and structure of the indicative HMPs list*

All ECHA data sources include substances which can potentially serve as an active medicinal product ingredient in HMPs. The ECHA database has therefore been filtered by CMR substances category 1A and 1B and crossed with the EMA data. As a result, a list with HMPs containing substances having a harmonised classification / self-classified classification in accordance with Regulation (EC) No 1272/2008 and being authorised as medicines in the EU and EEA has been established.

Since the NIOSH list is considered as a reputable source, substances fulfilling the definition mentioned under section 2. of this document and being also part of the 2020 NIOSH list are presented separately in Annex 1. In addition, and while avoiding duplication, the harmonised and self-classified substances which are not part of the 2020 NIOSH list are included in Annex 2.

([16]) Companies are responsible for collecting information on the properties and uses of the substances they manufacture or import above one tonne a year. They also have to assess the hazards and potential risks presented by the substance. This information is communicated to ECHA through a registration dossier containing the hazard information and, where relevant, an assessment of the risks that the use of the substance may pose and how these risks should be controlled.

([17]) Manufacturer or importer in determined cases has to notify a substance to the C&L inventory within one month from being placed on the market.

([18]) This database contains classification and labelling information on notified and registered substances received from manufacturers and importers. This also covers substances that are subject to harmonised classification.

([19]) In accordance with Article 5 of CLP regulation, manufacturers, importers and downstream users of a substance shall identify all the relevant available information for the purposes of determining whether that substance entails any hazards and examine that data accordingly.

([20]) Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30/04/2004, p. 1).

The final indicative HMPs list has 2 annexes and 4 tables corresponding to the different information sources:

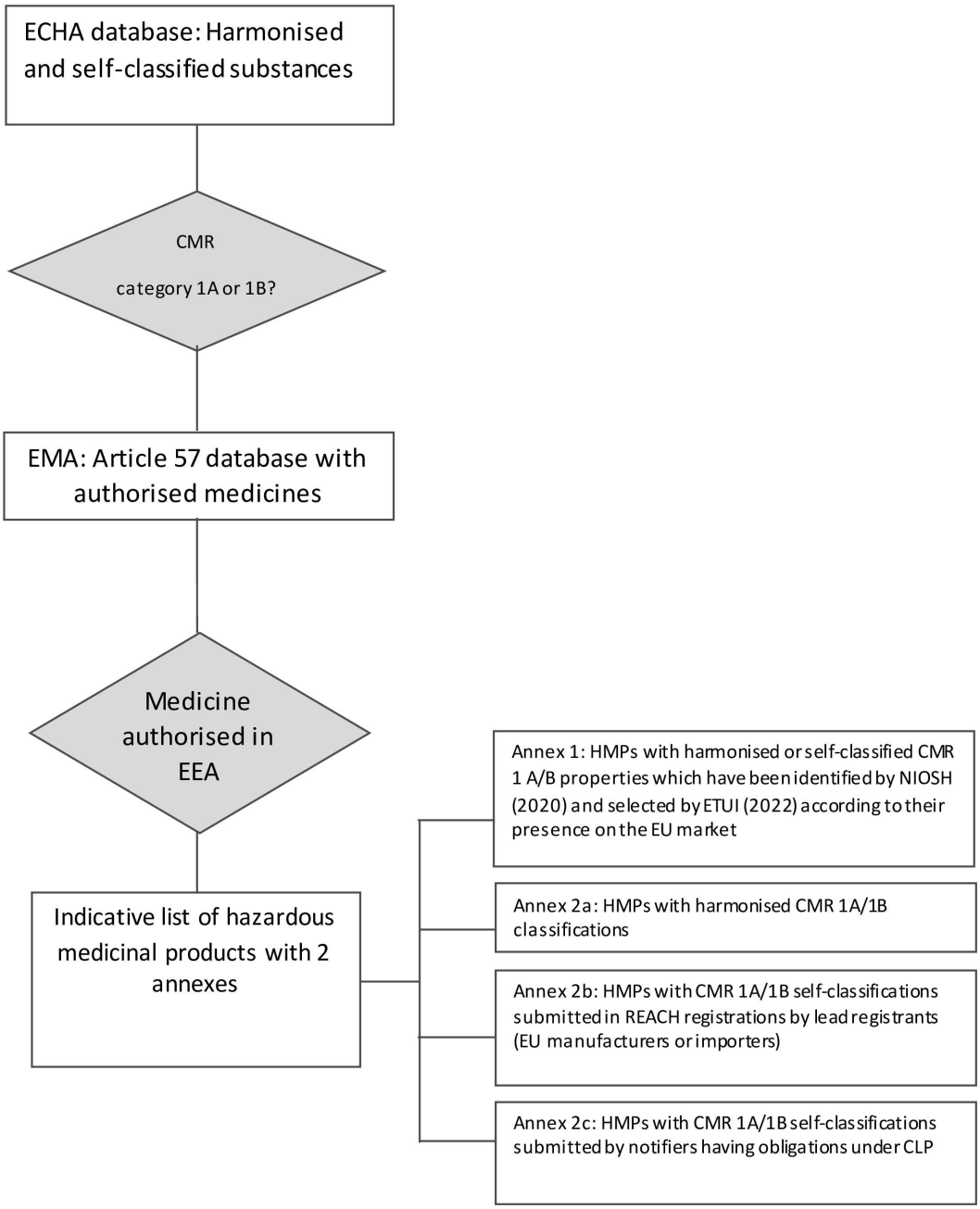
Annex 1: lists HMPs with harmonised or self-classified CMR 1 A/B properties which have been identified by NIOSH (2020) and selected by ETUI (2022) according to their presence on the EU market

Annex 2a: lists HMPs with harmonised CMR 1A/1B classifications ([21])

Annex 2b: lists HMPs with CMR 1A/1B self-classifications submitted in REACH registrations by lead registrants (EU manufacturers or importers)

Annex 2c: lists HMPs with CMR 1A/1B self-classifications submitted by notifiers having obligations under CLP

Figure 1 describes the underlying methodological approach.



([21]) Including RoI substances, see paragraph 3.2.1.1.

The resulting annexes and tables present the information in the following columns:

— Active medicinal product ingredient (name of the hazardous substance): where applicable, the name of the chemical salt/hydrated form of the substance is indicated in brackets.

— EC number (European Community Number- as published in the EU official Journal): where applicable, the EC number corresponds to the relevant form (in brackets).

— CAS RN (Chemical Abstracts Service Registry Number): where applicable, the CAS RN corresponds to the relevant form (in brackets).

— Therapeutic class (as listed in the Anatomical Therapeutic Chemical (ATC) ([22]) classification system.

— Muta 1A/1B classification: indicates the classification as Mutagen following the definition under the CLP Regulation.

— Carc 1A/1B classification: indicates the classification as Carcinogen following the definition shown under the CLP Regulation.

— Repr 1A/1B classification: indicates the classification as Reprotoxic following the definition shown under the CLP Regulation.

— EU classification (only Annex 1): indicates which EU classification the NIOSH substance bears.

— Number of notifiers vs. total (only Annex 2c): indicates how many notifiers have self-classified the substance as CMR 1A/1B and puts it in relation to the total number of notifiers. Note: this data gives an indication about the representativeness of the information among EU actors.

3.2.4. ***Principles and limitations of the methodological approach***

This methodological approach is based on the following principles:

1. Consistent with the definition under section 2, any substance with a CMR category 1 A/B (self-)classification was included.

2. If a substance has a harmonised classification related only to non-CMR properties; it is acknowledged that the CMR properties may not have been assessed during the Harmonised classification and labelling (CLH) process. However, information may exist that led EU actors to also self-classify the substance as CMR category 1A/1B and therefore these substances are included in Annex 2b or 2c.

3. If a substance has a harmonised CMR classification, any additional CMR self-classifications are not duplicated as the harmonised CMR classification prevails.

4. In Annex 2a, for reliability reasons, substances with the Note N have been excluded. For substances marked with a Note N in the Annex VI of CLP, the classification of the substance depends on the content and level of some impurities classified as CMR 1A/1B. Considering that the substances used in the production of medicinal products need to respect the high quality standards indicated in the European Pharmacopoeia which leads to very low levels of impurities, the non-CMR classification indicated in the ECHA database, and not the CMR classification due to impurities, should be considered.

5. In Annex 2b, only information submitted by lead registrants has been included; this is to increase the reliability of the information provided.

6. In Annex 2c, only substances with a ratio of ≥ 50 % of notifiers (submitting self-classification for CMR 1A/B properties) compared to the total number of notifiers have been included; this is to increase the reliability of the information provided. By doing so, 201 substances have been discarded from the original pool of substances.

([22]) ATC classification system: the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. It has to be noted that the list includes, in line with the definition mentioned under section 2., also classes like diagnostic agents or nutrients or mineral supplements which do not exhibit direct pharmaceutical effects.

7. To optimize the entries, some HMPs which are other forms of a parent compound, and which have both the same properties and the same therapeutic class (e.g. salts, hydrate forms, conjugated forms) have been removed from the annexes. The parent compound only has been kept in the annexes. This is the case for the following parent compounds: beclomethasone, betamethasone, cobalt (II) chloride, cyclophosphamide, estradiol, etoposide, ganirelix, hydrocortisone, leuprorelin, methotrexate, methylprednisolone, norethisterone, pemetrexed, perindopril, prednisolone, progesterone, retinol, sorafenib, tamoxifen, testosterone, topotecan.

   Users of the indicative list are advised to check whether other kind of forms (e.g. salts, hydrate forms, conjugated forms) listed in the annexes are relevant to them.

8. As medicinal products are excluded from the CLP requirements, they are not systematically evaluated under CLP. Thus, some relevant medicinal products may be missing from this HMP list because of a lack of incentive to self-classify them under the CLP.

9. New HMPs are constantly brought to the market, removed from the market or have their authorisation withdrawn. Therefore, this list can only reflect the information available at the date of its creation (June 2024).

ANNEX 1

HMPs with harmonised or self-classified CMR 1 A/B properties which have been identified by NIOSH (2020) and selected by ETUI (2022) according to their presence on the EU market

Active medicinal product ingredient	EC Number	CAS RN	Therapeutic class	EU (self-) - classification (H, R, N) (1)	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B
Abacavir	620-487-9	136470-78-5	Direct acting antivirals	R			X
Acitretin	259-474-4	55079-83-9	Antipsoriatics for systemic use	N			X
Alitretinoin / retinoic acid	610-929-9	5300-03-8	Other dermatological preparations	N			X
Arsenic trioxide	215-481-4	1327-53-3	Other antineoplastic agents	H		X	
Axitinib	638-771-6	319460-85-0	Protein kinase inhibitors	N			X
Azacitidine	206-280-2	320-67-2	Antineoplastic agents	N	X	X	X
Azathioprine	207-175-4	446-86-6	Immunosuppressants	N	X	X	X
Bendamustine (hydrochloride)	631-540-0	3543-75-7	Alkylating agents	N	X	X	X
Bicalutamide	618-534-3	90357-06-5	Hormone antagonists and related agents	N			X
Bleomycin (sulfate)	232-925-2	9041-93-4	Cytotoxic antibiotics and related substances	N	X	X	X
Bortezomib	605-854-3	179324-69-7	Other antineoplastic agents	N			X
Bosentan	643-099-1	147536-97-8	Antihypertensives	N			X
Busulfan	200-250-2	55-98-1	Alkylating agents	N	X	X	X
Cabazitaxel	680-632-7	183133-96-2	Antineoplastic agents	N			X
Cabozantinib (S-malate)	691-711-0	1140909-48-3	Antineoplastic agents	N			X
Capecitabine	604-948-1	154361-50-9	Antimetabolites	N		X	X
Carboplatin	255-446-0	41575-94-4	Other antineoplastic agents	N	X	X	X
Carmustine	205-838-2	154-93-8	Alkylating agents	N	X	X	X

Active medicinal product ingredient	EC Number	CAS RN	Therapeutic class	EU (self-) - classification (H, R, N) ([1])	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B
Cetrorelix (acetate)	685-963-0	145672-81-7	Pituitary and hypothalamic hormones and analogues	N			X
Chlorambucil	206-162-0	305-03-3	Alkylating agents	N	X	X	X
Chloramphenicol	200-287-4	56-75-7	Antibiotics for topical use	N	X	X	X
Chlormethine (hydrochloride)	200-246-0	55-86-7	Antineoplastic agents	N	X	X	X
Cisplatin	239-733-8	15663-27-1	Other antineoplastic agents	N	X	X	X
Clofarabine	631-422-9	123318-82-1	Antimetabolites	N			X
Colchicine	200-598-5	64-86-8	Antigout preparations	R	X		
Cyclophosphamide	200-015-4	50-18-0	Alkylating agents	N	X	X	X
Cyclosporine	611-907-1	59865-13-3	N.A.	N		X	X
Cytarabine	205-705-9	147-94-4	Antimetabolites	N	X		X
Dacarbazine	224-396-1	750512-03-9	Alkylating agents	N	X	X	
Dactinomycin	200-063-6	50-76-0	Cytotoxic antibiotics and related substances	N		X	X
Dasatinib (hydrate)	638-874-6	863127-77-9	Antineoplastic agents	N			X
Daunorubicin (hydrochloride)	245-723-4	23541-50-6	Cytotoxic antibiotics and related substances	N	X	X	X
Decitabine	219-089-4	2353-33-5	Antimetabolites	N	X		X
Diethylstilbestrol	200-278-5	56-53-1	Estrogens	N		X	X
Dinoprostone	206-656-6	363-24-6	Uterotonics	N			X
Docetaxel	601-339-2	114977-28-5	Plant alkaloids and other natural products	N	X	X	X
Doxorubicin hydrochloride	246-818-3	25316-40-9	Cytotoxic antibiotics and related substances	N	X	X	X
Dutasteride	638-758-5	164656-23-9	Urologicals	N			X
Entecavir monohydrate	606-668-5	209216-23-9	Antivirals for systemic use	N			X

Active medicinal product ingredient	EC Number	CAS RN	Therapeutic class	EU (self-) - classification (H, R, N) ([1])	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B
Enzalutamide	805-022-1	915087-33-1	Hormone antagonists and related agents	N			X
Epirubicin hydrochloride	260-145-2	56390-09-1	Cytotoxic antibiotics and related substances	N	X	X	X
Erlotinib (hydrochloride)	620-491-0	183319-69-9	Cytotoxic antibiotics and related substances	N			X
Estradiol	200-023-8	50-28-2	Estrogens	N		X	X
Estramustine (phosphate)	225-512-3	4891-15-0	Other antineoplastic agents	N			X
Estrogens conjugated	235-199-5	12126-59-9	Estrogens	N		X	X
Etoposide	251-509-1	33419-42-0	Plant alkaloids and other natural products	N	X	X	X
Exemestane	643-090-2	107868-30-4	Endocrine therapy	N			X
Finasteride	620-534-3	98319-26-7	Other dermatological preparations	N			X
Fluconazole	627-806-0	86386-73-4	Antifungals for topical use	N			X
Fludarabine (phosphate)	616-242-0	75607-67-9	Antineoplastic agents	N		X	X
Fluorouracil	200-085-6	51-21-8	Antimetabolites	R	X		X
Flutamide	236-341-9	13311-84-7	Hormone antagonists and related agents	N			X
Fulvestrant	642-998-6	129453-61-8	Hormone antagonists and related agents	N			X
Ganciclovir	627-054-3	82410-32-0	Direct acting antivirals	N			X
Ganirelix	689-234-8	124904-93-4	Hypothalamic hormones	N			X
Gemcitabine	619-100-6	95058-81-4	Antimetabolites	N			X
Goserelin	686-281-6	65807-02-5	Endocrine therapy	N			X
Hydroxycarbamide	204-821-7	127-07-1	Other antineoplastic agents	N	X		X

ELI: http://data.europa.eu/eli/C/2025/1150/oj

Active medicinal product ingredient	EC Number	CAS RN	Therapeutic class	EU (self-) - classification (H, R, N) ([1])	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B
Idarubicin (hydrochloride)	260-990-7	57852-57-0	Cytotoxic antibiotics and related substances	N	X	X	X
Ifosfamide	223-237-3	3778-73-2	Alkylating agents	N	X	X	X
Imatinib	604-855-6	152459-95-5	Protein kinase inhibitors	R			X
Irinotecan (hydrochloride)	603-967-2	136572-09-3	Plant alkaloids and other natural products	N	X		X
Isotretinoin	225-296-0	4759-48-2	Anti-acne preparations for topical use	N			X
Ivabradine (hydrochloride)	638-798-3	148849-67-6	Cardiac therapy	N			X
Ixazomib (citrate)	813-102-2	1239908-20-3	Antineoplastic agents	N			X
Lenalidomide	691-297-1	191732-72-6	Immunosuppressants	N			X
Letrozole	675-034-8	112809-51-5	Hormone antagonists and related agents	N			X
Leuprorelin	633-395-9	53714-56-0	Hormones and related agents	N			X
Lomustine	235-859-2	13010-47-4	Alkylating agents	N	X	X	X
Medroxyprogesterone acetate	200-757-9	71-58-9	Hormonal contraceptives for systemic use	N	X		X
Megestrol (acetate)	209-864-5	595-33-5	Hormonal contraceptives for systemic use	N		X	X
Melphalan	205-726-3	148-82-3	Alkylating agents	N	X	X	X
Methotrexate	200-413-8	59-05-2	Antimetabolites	N	X		X
Methylergometrine (maleate)	260-734-4	57432-61-8	Other gynecologicals	N			X
Mifepristone	617-559-7	84371-65-3	Other sex hormones and modulators of the genital system	N			X
Misoprostol	664-288-5	59122-46-2	Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)	N			X
Mitomycin	200-008-6	50-07-7	Cytotoxic antibiotics and related substances	N	X	X	X

Active medicinal product ingredient	EC Number	CAS RN	Therapeutic class	EU (self-) - classification (H, R, N) ([1])	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B
Mitotane	200-166-6	53-19-0	Other antineoplastic agents	N			X
Mitoxantrone (dihydrochloride)	274-619-1	70476-82-3	Cytotoxic antibiotics and related substances	N	X	X	X
Mycophenolate mofetil	627-027-6	128794-94-5	Immunosuppressants	N			X
Mycophenolic acid	246-119-3	24280-93-1	Immunosuppressants	R			X
Nelarabine	642-916-9	121032-29-9	Antimetabolites	N			X
Nilotinib	700-544-5	641571-10-0	Antineoplastic agents	N			X
Olaparib	642-941-5	763113-22-0	Other antineoplastic agents	N			X
Oxaliplatin	621-248-1	61825-94-3	Other antineoplastic agents	N	X	X	X
Paclitaxel	608-826-9	33069-62-4	Plant alkaloids and other natural products	N		X	X
Panobinostat	803-814-1	404950-80-7	Other antineoplastic agents	N			X
Pazopanib (hydrochloride)	619-728-0	635702-64-6	Antineoplastic agents	N			X
Pemetrexed	680-625-9	137281-23-3	Antimetabolites	N			X
Phenytoin	200-328-6	57-41-0	Antiepileptics	R			X
Pomalidomide	805-902-5	19171-19-8	Immunosuppressants	N			X
Procarbazine (hydrochloride)	206-678-6	366-70-1	Other antineoplastic agents	N	X	X	X
Progesterone	200-350-6	57-83-0	Progestogens	N	X	X	X
Raloxifene (hydrochloride)	639-789-7	82640-04-8	Other sex hormones and modulators of the genital system	N			X
Regorafenib	815-051-1	755037-03-7	Protein kinase inhibitors	N			X
Ribavirin	636-825-3	36791-04-5	Direct acting antivirals	N			X
Sorafenib	608-209-4	284461-73-0	Protein kinase inhibitors	N			X

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Active medicinal product ingredient	EC Number	CAS RN	Therapeutic class	EU (self-) - classification (H, R, N) ([1])	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B
Spironolactone	200-133-6	52-01-7	Aldosterone antagonists and other potassium-sparing agents	N			X
Streptozocin	242-646-8	18883-66-4	Alkylating agents	N	X	X	X
Sunitinib (malate)	638-825-9	341031-54-7	Antineoplastic agents	N			X
Tamoxifen	234-118-0	10540-29-1	Hormone antagonists and related agents	R		X	X
Temozolomide	630-358-9	85622-93-1	Alkylating agents	N	X		X
Temsirolimus	686-177-0	162635-04-3	Protein kinase inhibitors	N			X
Testosterone	200-370-5	58-22-0	Androgens	R			X
Thalidomide	200-031-1	50-35-1	Immunosuppressants	N			X
Thiotepa	200-135-7	52-24-4	Alkylating agents	N	X	X	X
Tioguanine	205-827-2	154-42-7	Antimetabolites	N	X	X	X
Tofacitinib	689-145-4	477600-75-2	Immunosuppressants	N			X
Topotecan	687-471-1	123948-87-8	Antineoplastic agents	N	X		
Trametinib	629-899-3	871700-17-3	Protein kinase inhibitors	N			X
Trastuzumab emtansine	854-470-4	1018448-65-1	Monoclonal antibodies and antibody drug conjugates	N	X		X
Treosulfan	206-081-0	299-75-2	Antineoplastic agents	N		X	
Tretinoin	206-129-0	302-79-4	Anti-acne preparations for topical use	N			X
Triptorelin (palmoate)	689-181-0	124508-66-3	Endocrine therapy	N			X
Ulipristal (acetate)	682-170-1	126784-99-4	Sex hormones and modulators of the genital system	N			X
Urofollitropin	686-287-9	146479-72-3	Sex hormones and modulators of the genital system	N			X

Active medicinal product ingredient	EC Number	CAS RN	Therapeutic class	EU (self-) - classification (H, R, N) ([1])	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B
Valganciclovir (hydrochloride)	641-360-4	175865-59-5	Antivirals for systemic use	N	X	X	X
Valproate semisodium / Sodium valproate / Valproic acid	630-325-9 / 213-961-8 / 202-777-3	76584-70-8 / 1069-66-5 / 99-66-1	Antiepileptics	N / N / R			X
Vandetanib	669-841-4	443913-73-3	Protein kinase inhibitors	N			X
Vinorelbine (tartrate)	639-264-2	125317-39-7	Plant alkaloids and other natural products	N	X	X	X
Voriconazole	629-701-5	137234-62-9	Antimycotics for systemic use	N			X
Warfarin (sodium)	204-929-4	129-06-6	Antithrombotic agents	N			X
Zidovudine	623-849-4	30516-87-1	Antivirals for systemic use	N		X	

([1]) H=Harmonised, R=Registration, N=Notification.

ANNEX 2a

HMPs with harmonised CMR 1A/1B classifications

Active medicinal product ingredient	EC Number	CAS RN	Therapeutic class	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B
4,4′-Methylenedianiline	202-974-4	101-77-9	Other diagnostic agents		X	
Borax	215-540-4	1303-96-4	stomatological preparations			X
Boric acid	233-139-2	10043-35-3	Antiinfectives			X
Carbon monoxide	211-128-3	630-08-0	Other diagnostic agents			X
Coal tar	232-361-7	8007-45-2	Antipsoriatics for topical use		X	
Cobalt	231-158-0	7440-48-4	Other nutrients		X	X
Cobalt(II) chloride	231-589-4	7646-79-9	Other diagnostic agents		X	X
Creosote	232-287-5	8001-58-9	Expectorants, excl. combinations with cough suppressants		X	X (Notification)
Formaldehyde	200-001-8	50-00-0	Other diagnostic agents		X	
Hydrazine sulfate	233-110-4	10034-93-2	Other diagnostic agents		X (RoI)	
Kalium bichromicum	231-906-6	7778-50-9	Other diagnostic agents	X	X	X
Ketoconazole	265-667-4	65277-42-1	Antifungals for topical use			X
Methylrosanilinium chloride	208-953-6	548-62-9	Antiseptics and disinfectants		X	
Nickel gluconate	276-205-6	71957-07-8	Other mineral supplements		X	X
Nickel sulfate	232-104-9	7786-81-4	Other diagnostic agents		X	X
Oxyquinoline	205-711-1	148-24-3	Stomatological preparations			X

Active medicinal product ingredient	EC Number	CAS RN	Therapeutic class	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B
Pentetic acid	200-652-8	67-43-6	Renal system			X
Phenolphthalein	201-004-7	77-09-8	Drugs for constipation		X	
Pyrithione zinc	236-671-3	13463-41-7	Other dermatological preparations			X
Sodium borate	215-540-4	1330-43-4	Antiinfectives			X
Sodium perborate	239-172-9	7632-04-4	Stomatological preparations			X
Theophylline	200-385-7	58-55-9	Other systemic drugs for obstructive airway diseases			X

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ANNEX 2b

HMPs with CMR 1A/1B self-classifications submitted in REACH registrations by lead registrants (EU manufacturers or importers)

Active medicinal product ingredient	EC number	CAS RN	ATC Level 3	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B
Benzaldehyde	202-860-4	100-52-7	Other diagnostic agents			X
Betamethasone	206-825-4	378-44-9	Intestinal antiinflammatory agents			X
Clindamycin hydrochloride	244-398-6	21462-39-5	Anti-acne preparations for topical use			X
Copper sulfate	231-847-6	7758-98-7	All other therapeutic products		X	X
Dapsone	201-248-4	80-08-0	Anti-acne preparations for topical use			X
Dimethyl-4-toluidine	202-805-4	99-97-8	Other diagnostic agents		X	
Ethyl chloride	200-830-5	75-00-3	Anesthetics, local			X
Hydrocortisone	200-020-1	50-23-7	Stomatological preparations			X
Methylene-bis(methyloxazolidine)	266-235-8	66204-44-2	Other diagnostic agents		X	
Methylprednisolone	201-476-4	83-43-2	Corticosteroids, plain			X
Metronidazole	207-136-1	443-48-1	Stomatological preparations		X	
Norethisterone	200-681-6	68-22-4	Hormonal contraceptives for systemic use			X
Nutmeg	282-013-3	84082-68-8	Other diagnostic agents		X	
Prasterone	200-175-5	53-43-0	Anabolic steroids			X
Prednisolone	200-021-7	50-24-8	Stomatological preparations			X

Active medicinal product ingredient	EC number	CAS RN	ATC Level 3	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B
Retinol	200-683-7	68-26-8	Anti-acne preparations for topical use			X
Retinyl acetate	204-844-2	127-47-9	Vitamin A and D, incl. combinations of the two			X
Shale oil	269-646-0	68308-34-9	Antiseptics and disinfectants	X	X	X
Silver nitrate	231-853-9	7761-88-8	Antiseptics and disinfectants			X

ELI: http://data.europa.eu/eli/C/2025/1150/oj

ANNEX 2c

HMPs with CMR 1A/1B self-classifications submitted by notifiers having obligations under CLP

As explained above, the reliability of data linked to self-classifications is considered to be lower compared to that from the harmonised classification. Therefore, in case of uncertainty, it is recommended that the employer contacts the company in charge of the release of the given HMP on the market, to obtain additional information (Material Safety Data Sheet or similar document) concerning the classification of the substance.

A column indicates how many notifiers have self-classified the substance as CMR 1A/1B and puts it in relation to the total number of notifiers. This data gives an indication about the representativeness and reliability of the information. In annex 2c, for reliability reasons, only substances with a ratio of ≥ 50 % of notifiers indicating CMR 1A/B characteristics compared to the total number of notifiers have been included.

Active medicinal product ingredient	EC number	CAS RN	Therapeutic class	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B	#notifiers (vs total) (ECHA C&L inventory)
Acenocoumarol	205-807-3	152-72-7	Antithrombotic agents			X	6 (9)
Acetohydroxamic acid	208-913-8	546-88-3	Urologicals			X	7 (10)
Amikacin	253-538-5	37517-28-5	Antibiotics for topical use			X	1 (2)
Anagrelide	864-866-9	68475-42-3	Other antineoplastic agents			X	1 (1)
Anastrozole	601-715-6	120511-73-1	Hormone antagonists and related agents			X	12 (17)
Apalutamide	807-449-9	956104-40-8	Hormone antagonists and related agents		X		2 (4)
Baricitinib	691-421-4	1187594-09-7	Immunosuppressants			X	3 (5)
Bazedoxifene	805-732-1	198481-32-2	Other sex hormones and modulators of the genital system			X	1 (1)
Beclometasone dipropionate	226-886-0	5534-09-8	Intestinal antiinflammatory agents			X	12 (22)
Botulinum toxin type E	297-258-1	93384-47-5	Muscle relaxants, peripherally acting agents			X	1 (2)
Buserelin acetate	636-185-5	68630-75-1	Hormones and related agents			X	6 (7)
Chlormadinone acetate	206-118-0	302-22-7	Progestogens			X	7 (9)

Active medicinal product ingredient	EC number	CAS RN	Therapeutic class	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B	#notifiers (vs total) (ECHA C&L inventory)
Cimetidine	257-232-2	51481-61-9	Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)			X	8 (16)
Clobetasol propionate	246-634-3	25122-46-7	Corticosteroids, plain			X	12 (22)
Clomifene citrate	200-035-3	50-41-9	Gonadotropins and other ovulation stimulants			X	6 (12)
Corifollitropin alfa	692-844-7	195962-23-3	Gonadotropins and other ovulation stimulants			X	2 (2)
Cyproterone	690-915-7	2098-66-0	Antiandrogens			X	1 (1)
Danazol	241-270-1	17230-88-5	Other sex hormones and modulators of the genital system			X	4 (8)
Desflurane	688-023-8	57041-67-5	Anesthetics, general			X	2 (4)
Desogestrel	258-929-4	54024-22-5	Hormonal contraceptives for systemic use			X	8 (11)
Dexmedetomidine	601-281-8	113775-47-6	Hypnotics and sedatives			X	1 (1)
Diflucortolone valerate	261-655-8	59198-70-8	Corticosteroids, plain			X	3 (6)
Dronedarone	604-240-2	141626-36-0	Antiarrhythmics, class i and iii			X	2 (4)
Drospirenone	266-679-2	67392-87-4	Hormonal contraceptives for systemic use			X	10 (15)
Duvelisib	813-697-9	1201438-56-3	Protein kinase inhibitors			X	1 (1)
Efavirenz	620-492-6	154598-52-4	Direct acting antivirals			X	9 (17)
Encorafenib	815-119-0	1269440-17-6	Protein kinase inhibitors			X	1 (2)
Estetrol	840-340-4	15183-37-6	Other dermatological preparations			X	3 (4)

Active medicinal product ingredient	EC number	CAS RN	Therapeutic class	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B	#notifiers (vs total) (ECHA C&L inventory)
Estriol	200-022-2	50-27-1	Estrogens		X	X	3 (9) - 7 (9)
Ethambutol dihydrochloride	213-970-7	1070-11-7	Drugs for treatment of tuberculosis			X	5 (7)
Etonogestrel	258-936-2	54048-10-1	Hormonal contraceptives for systemic use			X	10 (10)
Flecainide acetate	258-997-5	54143-56-5	Antiarrhythmics, class i and iii			X	7 (9)
Fluocortolone caproate	206-140-0	303-40-2	Agents for treatment of hemorrhoids and anal fissures for topical use			X	1 (2)
Fluocortolone pivalate	249-504-4	29205-06-9	Agents for treatment of hemorrhoids and anal fissures for topical use			X	1 (2)
Fluticasone furoate	629-894-6	397864-44-7	Decongestants and other nasal preparations for topical use			X	7 (12)
Fotemustine	630-468-7	92118-27-9	Alkylating agents	X	X	X	1 (2) - 1 (2) - 1 (2)
Furosemide	200-203-6	54-31-9	High-ceiling diuretics		X	X	1 (50) - 28 (50)
Gentamicin	215-765-8	1403-66-3	Antibiotics for topical use			X	4 (6)
Griseofulvin	204-767-4	126-07-8	Antifungals for topical use	X	X	X	3 (20) - 1 (20) - 16 (20)
Hydroxyzine	200-693-1	68-88-2	Anxiolytics			X	1 (1)
Interferon beta-1B	682-322-7	145155-23-3	Antiinfectives			X	2 (2)
Iron(III)-hydroxide dextran complex	618-390-1	9004-66-4	Iron preparations		X		3 (4)
Kanamycin sulfate	246-933-9	25389-94-0	Intestinal antiinfectives			X	23 (28)
Levonorgestrel	212-349-8	797-63-7	Hormonal contraceptives for systemic use			X	8 (12)
Lisinopril	278-488-1	76547-98-3	ACE inhibitors, plain			X	4 (7)
Lormetazepam	212-700-5	848-75-9	Hypnotics and sedatives			X	2 (3)

Active medicinal product ingredient	EC number	CAS RN	Therapeutic class	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B	#notifiers (vs total) (ECHA C&L inventory)
Luteinising hormone	232-661-8	9002-67-9	Gonadotropins and other ovulation stimulants			X	2 (2)
Lynestrenol	200-151-4	52-76-6	Hormonal contraceptives for systemic use	X		X	1(3) - 2 (3)
Metenolone enantate	206-141-6	303-42-4	Anabolic steroids			X	1 (1)
Methylprednisolone aceponate	658-084-5	86401-95-8	Corticosteroids, plain			X	4 (5)
Mycophenolate sodium	687-703-1	37415-62-6	Immunosuppressants			X	2 (3)
Nandrolone decanoate	206-639-3	360-70-3	Anabolic steroids			X	6 (10)
Netilmicin sulfate	260-147-3	56391-57-2	Aminoglycoside antibacterials			X	7 (9)
Nilutamide	624-700-6	63612-50-0	Hormone antagonists and related agents			X	3 (4)
Niraparib tosilate monohydrate	855-068-1	1613220-15-7	Other antineoplastic agents	X		X	2 (3) - 1 (3)
Nomegestrol acetate	261-379-8	58652-20-3	Progestogens			X	6 (12)
Perindopril	617-394-0	82834-16-0	ACE inhibitors, plain			X	1 (1)
Phenazepam	682-231-2	51753-57-2	Anxiolytics	X		X	2 (4) - 2 (4)
Phenobarbital	200-007-0	50-06-6	Antiepileptics			X	19 (25)
Pirtobrutinib	864-730-9	2101700-15-4	Protein kinase inhibitors			X	4 (4)
Podophyllum resin	232-546-2	9000-55-9	Drugs for constipation			X	8 (8)
Rosuvastatin	689-191-5	287714-41-4	Lipid modifying agents, plain			X	1 (1)
Sacituzumab govitecan	872-125-6	1491917-83-9	Monoclonal antibodies and antibody drug conjugates			X	1 (1)
Selpercatinib	843-660-2	2152628-33-4	Protein kinase inhibitors			X	3 (3)

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Active medicinal product ingredient	EC number	CAS RN	Therapeutic class	Muta 1A/1B	Carc 1A/1B	Repr 1A/1B	#notifiers (vs total) (ECHA C&L inventory)
Sodium perborate	239-172-9	7632-04-4	Stomatological preparations			X	5 (5)
Sulprostone	262-173-0	60325-46-4	Uterotonics			X	4 (4)
Talazoparib	815-271-8	1207456-01-6	Other antineoplastic agents			X	1 (1)
Tegafur	241-846-2	17902-23-7	Antimetabolites			X	2 (4)
Timolol	248-032-6	26839-75-8	Beta blocking agents			X	1 (1)
Triamcinolone acetonide	200-948-7	76-25-5	Stomatological preparations			X	10 (17)
TriamcinoDlone acetonide dipotassium phosphate	217-537-3	1881-20-5	Stomatological preparations			X	1 (1)
Trofosfamide	244-770-8	22089-22-1	Alkylating agents	X	X	X	1 (1) - 1 (1) - 1 (1)