ROMANIA

Newsletter

Year 22, No. 3 (87), 3rd quarter of 2020

National Agency for Medicines and Medical Devices of Romania

Orders of the Minister of Health

Medicinal product batches recalled during the 3rd quarter of 2020

Applications for marketing authorisation/marketing authorisation renewal received during the 2nd quarter of 2020

Medicinal products authorised for marketing during the 2nd quarter of 2020

EMA centrally authorised medicinal products notified for marketing in Romania during the 2nd quarter of 2020

ISSN 1583-347X

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Order no. 1.353
of 30 July 2020

on amendment and supplementation of Order of the Minister of Health no. 861/2014 on approval of criteria and methodology for assessment of health technologies, of documentation to be submitted by applicants, methodological means used in the assessment for inclusion, extension of indications, non-inclusion into or exclusion from the List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programs, as well as the means for appeal thereof

Published in: the Official Gazette of Romania no. 687 of 31 July 2020

On seeing Approval Report no. NT 6.326 of 30.07.2020 of the Pharmaceutical and Medical Devices Directorate and notification no. 50.685E of 21 January 2020 of the National Agency for Medicines and Medical Devices, registered at the Ministry of Health with no. REG 2/517 of 22 January 2020,

taking into account provisions of Article 243 of Law 95/2006 on healthcare reform, republished, as further amended and supplemented,

taking into account provisions of Article 2 i) and Article 4 (5) 1 of Law no. 134/2019 on reorganisation of the National Agency for Medicines and Medical Devices and amendment of further ruling provisions,

based on Article 7 (4) of Government Decision no. 144/2010 on the organisation and operation of the Ministry of Health, as further amended and supplemented,

the minister of health hereby issues the following Order:

Art. I – Order of the Minister of Health no. 861/2014 on approval of criteria and methodology for assessment of health technologies, of documentation to be submitted by applicants, methodological means used in the assessment for inclusion, extension of indications, non-inclusion into or exclusion from the List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programs, as well as the means for appeal thereof, published in the Official Gazette of Romania, Part I, no. 557 of 28 July 2014, as further amended and supplemented, is amended and shall read as follows:

1. Article 8 c) is amended and shall read as follows:

"c) New INNs, other than those for which applicants have submitted an application; The National Agency for Medicines and Medical Devices of Romania (NAMMDR) will notify marketing authorisation holders (MAHs) at least 10 working days before initiation of the evaluation procedure. The NAMMDR shall publish the list of products for which the ex officio evaluation procedure has been initiated on the NAMMDR website;".

2. A new Article, namely Article 8(1), is introduced after Article 8, as follows:

"Art. 8(1) - The NAMMDR will initiate the procedure for evaluating the reimbursed INNs in the List in order to move / exclude or mark / eliminate the ranking with (*), (**) (**1), for those medicinal products for which the specialised commissions within the Ministry of Health or the National Health Insurance House have notified the prescription outside the approved therapeutic indications or the exclusion of the medicinal product from the therapeutic guidelines with an impact on the FNUASS budget or for prescribed medicinal products that do not have a therapeutic protocol, respecting the indications, doses and contraindications in CPR, within the competence of the prescriber."

3. Annex 1, Article 1, points c), k), l), n) and p) are amended and shall read as follows:

"c) comparator – an INN included in the List of INNs of on-prescription medicinal products provided to insurants within the healthcare insurance system, irrespective of personal contribution, within the social health insurance system, as well as INNs relating to medicinal products provided in the frame of national healthcare programs, approved through Government Decision no. 720/2008, republished, with the same approved indication, meant for the same population group/subgroup as INNs assessed, as required. A product already reimbursed on the basis of cost-volume or cost-volume-result contracts can be considered as a comparator exclusively by comparing the prices available in CANAMED at the time of submission of the assessment dossier. If the comparator is a reimbursed product based on a cost-volume or cost-volume-result contract, the medicinal product subject to evaluation will be able to benefit from conditional reimbursement at most, even if the final score obtained as a result of the evaluation process would allow unconditional inclusion;

.....

k) reimbursement status – the entire body of information concerning inclusion of a medicinal product into the sublists and sections provided in the List, the reimbursement percentage, manner of prescription; changes in reimbursement status of a reimbursable INN include: relocation, addition, exclusion or removal/addition of the (*), (**)1, or (**)2 ranking; the determination of the level of reimbursement for medicinal products whose indications are not limited to the categories of chronic diseases or national health programmes described in sub-list C, sections C1 and C2 of the List shall be carried out as follows: the cost of treatment / year is calculated, the minimum monthly cost is established, the level of the patient's monthly personal contribution is established on the "percentage" of reimbursement related to sublists A, B and D of the minimum monthly cost; the maximum amount of indebtedness is established by applying 20% to the minimum gross income in force at the valuation

date; if the personal contribution on the 20% clearing level is greater than or equal to 50% of the maximum amount of indebtedness, the next level of clearing is analysed; if the personal contribution at the 20% clearing level is less than 50% of the maximum amount owed, the product shall be included in sublist D; if the personal contribution on the 50% clearing level is greater than or equal to 50% of the maximum amount owed, the next level of clearing shall be considered; if the personal contribution at the 50% clearing level is less than 50% of the maximum amount owed, the product shall be included in sublist B; if the personal contribution at the 90% clearing level is greater than or equal to 50% of the maximum amount owed, the product shall be included at the 100% clearing level in a section of sublist C; if the personal contribution at the 90% clearing level is less than 50% of the maximum amount owed, the product shall be included in sublist A;

l) extension of indication – addition of a new pathology/disease for which the respective medicinal product with reimbursable INN has demonstrated safety and efficacy, included in the Summary of Product Characteristics reviewed by the European Medicinal products Agency or the National Agency for Medicines and Medical Devices of Romania;

.....

n) addition - inclusion in the same indication of another strength, another pharmaceutical form, a new population segment, modification of the line of treatment, inclusion of a new line of treatment for the medicinal product with a reimbursed INN, included in the List based on the assessment of medical technologies;

.....

p) removal/addition of the (*), (**)1 , or (**)2 ranking – change of conditions for prescriptions of treatment with medicinal products corresponding to reimbursable International Non-proprietary Names included in the List;

4. In Annex 1, under Article 1, a new point is introduced after point ab), point ac), which reads as follows:

"ac) advanced therapy medicinal product – a product defined otherwise than in line with Article 2 of Regulation (EC) no. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 and of Directive of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use."

5. In Annex 1, under Article 5, points c) and d) are repealed.

6. In Annex 1, two new Articles are introduced after Article 5, Articles 6 and 7, which read as follows:

"Art. 6 - The evaluation criteria provided in Table 41 apply to the following situations:

a) generics without reimbursable INNs in the List;

b) biosimilars without reimbursable INNs in the List.

Art. 7 - The evaluation criteria provided in Table 9 apply in the following situations:

a) medicinal products corresponding to already reimbursed INNs with decisions for conditional inclusion, with ongoing cost-volume/cost-volume-result contracts, which have cumulatively lost data exclusivity and no longer benefit from patent protection and/or certificates for additional protection and their generic / generics meet/meets the marketing conditions on the Romanian territory;

b) medicinal products corresponding to already reimbursed INNs with decisions for conditional inclusion, with ongoing cost-volume/cost-volume-result contracts, which have cumulatively lost data exclusivity and no longer benefit from patent protection and/or certificates for additional protection and whose biosimilar(s) meet the requirements on the Romanian territory."

7. In Annex 1, Table 1 is amended and shall read as follows:

"Table 1 - Criteria for addition of a reimbursable INN

No.	Criteria	Details
1.	Ensuring addressability for patients	It will be shown how to solve by adding the lack of access to treatment, compliance to treatment of certain categories of patients, population segments or disease stages.
2.	Proof of reimbursement in EU countries and Great Britain	Required to demonstrate the widespread use of the product in at least three Member States of the European Union and the United Kingdom and maintenance of a unified approach.
3.	Financial impact analysis	Shall be calculated in accordance with the methodology in Annex 2 to the Order.

NOTE:

1. For addition of another strength or pharmaceutical form related to the already assessed medicinal product, which is used within the same indication as the already assessed strength or pharmaceutical form, the positive assessment report is issued only for situations where this addition has a negative/neutral impact. In this case, the comparator is the medicinal product with the strength or pharmaceutical form corresponding to the already reimbursed INN included in the List based on the assessment of medical technologies.

2. In order to issue the decision to add to the List by the NAMMDR, for a new segment or population group / to modify the line of treatment / to include a new line of treatment for the medicinal product with a reimbursed INN, the criteria provided in no. 1 and 2 of Table 1 must be met cumulatively, and for the situation described under point 1, only the criterion provided in no. 3 of Table 1. "

8. In Annex 1, Table 2 is amended and shall read as follows:

Table 2 - Criteria for ranking reimbursed INNs as (*), (**)1 or (**)2

No.	Criteria	Details

1.	High cost INNs (i) prescribed and dispensed based on therapeutic protocols entered into the Electronic Register of the Health Insurance House of high-cost medicinal products under monitoring	(**)2 Treatment with medicinal products corresponding to INNs ranked (**)2 is conducted based on therapeutic protocols established by specialised commissions of the Ministry of Health, subject to monitoring through the Register of the Health Insurance House of high-cost medicinal products and/or started in non-interventional studies carried out in Romania, for collection of real-life data for HTA purposes
2.	Costly INN(s) and/or for which an additional monitoring is required both in terms of pharmacovigilance and administration, whose prescription is made by the appointed physician only on the basis of a therapeutic protocol	(**) Treatment for medicinal products corresponding to INNs ranked (**) shall be performed on the basis of therapeutic protocols issued by special commissions of the Ministry of Health. (**) 1 Treatment for medicinal products corresponding to INNs ranked (**) 1 shall be performed on the basis of therapeutic protocols issued by special commissions of the Ministry of Health and specific forms.
3.	Low-cost INNs (ii) requiring medical prescription according to SmPC	(*) Treatment with medicinal products corresponding to INNs ranked (*) shall be initiated by the appointed physician within the limits of competence and can further be prescribed by the family physician based on the medical letter issued by the medical specialist.

(i) Products whose calculated monthly treatment cost* is > 2 x GDP**/capita/month.

(ii) Medicinal products whose calculated monthly treatment cost*) is below the gross minimum salary on the date of issuance of the decision for inclusion in the List.

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*) * Monthly treatment cost - total price of the INN calculated at the maximum retail price level with VAT, included in the Index of prices of medicinal products for human use approved on assessment date, according to doses and administration duration as provided in the SmPC, for one calendar month. The monthly treatment cost is calculated for each strength, pharmaceutical form or route of administration of the respective INN. The (*), (**) 1 or (**) 2 ranking of reimbursed INNs depends on the pharmaceutical form with the highest monthly treatment cost.

* * GDP Reference: the National Institute of Statistics, the latest published Statistical Yearbook of Romania

9. In Annex 1, Table 3 is amended and shall read as follows:

"Table 3 - Assessment criteria for reimbursed INNs included into the List			
Assessment criteria	Rating	A single rating selected	Scores may be summated
1. HTA based on therapeutic benefit estimate (SMR)			
1.1. INN with major/important SMR level (as assessed by the HAS) (BT 1)	0	Not to exceed 30 points	
1.2. INN not assessed by the HAS	10		
1.3. INN with moderate/low SMR level (as assessed by the HAS) (BT 2)	15		
1.4. INN with insufficient SMR level (as assessed by the HAS) (BT 3) or withdrawn from the List of medicinal products reimbursed within the social insurance system in France	30		
2. Cost-efficacy based HTA - Great Britain (NICE/SMC)			
2.1. INN approved, with no restrictions, by the Great Britain health technologies assessment authority or for which the MAH/MAH representative submits an affidavit attesting free of restriction reimbursement in Great Britain, with restrictions compared with the SmPC, also following a NICE class assessment or assessment of other types of reports/reviews performed by the NHS and related documentation.	0	Not to exceed 30 points	
2.2. INN not assessed by the Great Britain authority for assessment of health technologies (NICE/SMC).	10		
2.3. INN approved upon review, with restrictions in relation with the SmPC, by the Great Britain authority for assessment of health technologies (NICE/SMC)	15		
2.4. INN not approved for inclusion in the reimbursement system by the Great Britain authority for assessment of health technologies (NICE/SMC)/for which approval for inclusion in the system has been withdrawn/included in the negative list of the Great Brittan National Healthcare Service (NHS)/has been withdrawn from the List of reimbursed medicinal products of the Great Brittan National Healthcare Service	30		
2.5. The INN has received a MA withdrawal decision.	50		
2.6. A INN for which the specialised commissions of the Ministry of Health informed the NAMMDR that there is no therapeutic benefit according to the analysis of existing documentation at European level or that the INN is no longer recommended in	30		

national/international clinical guidelines, as appropriate.			

10. In Annex 1, Table 4 is amended and shall read as follows:

" Table 4 - Assessment criteria for new INNs			
Assessment criteria	Rating	A single rating selected	Scores may be summated
1. HTA based on therapeutic benefit estimate (SMR)			
1.1. New INNs, reimbursable INNs with extension of indication, classified as BT1-major/important by the HAS	15	Not to exceed 15 points	
1.2. New INNs, reimbursable INNs with extension of indication, classified as BT2-moderate/low (nonetheless justifying reimbursement) by the HAS.	7		
1.3. New INNs, reimbursable INNs with extension of indication, classified as BT3 - insufficient according to HAS	0		
2. HTA based on cost-efficacy			
2.1. New INNs, reimbursable INNs with extension of indication, which have received a positive opinion, approved without restrictions in relation with the SmPC, by Great Britain authorities for assessment of health technologies (NICE/SMC) or for which the MAH/MAH representative submits an affidavit attesting free of restriction reimbursement in Great Britain, with restrictions compared with the SmPC, also following a NICE class assessment or assessment of other types of reports/reviews performed by the NHS and related documentation	15	Not to exceed 15 points	
2.2. New INNs, reimbursable INNs with extension of indication, which have received a positive opinion, with restrictions in relation with the SmPC, by Great Britain authorities for assessment of health technologies (NICE/SMC) or for which the MAH/MAH representative submits an affidavit attesting free of restriction reimbursement in Great Britain, with restrictions compared with the SmPC, also following a NICE class assessment or assessment of other types of reports/reviews performed by the NHS and related documentation	7		
2.3. New INNs, reimbursable INNs with extension of indication, care have received a negative opinion	0		

from the Great Britain authority for assessment of health technologies (NICE/SMC) or for which an assessment report has not been issued			
2.4. New INNs, reimbursable INNs with extension of indication, for which the assessment report of the authorities for assessment of medical technologies of Germany (IQWIG/G-BA) demonstrates an additional therapeutic benefit as opposed to the comparator (regardless of its size), approved without restrictions in relation with the SmPC and which are included into the GBA therapeutic guidelines and which have not been assessed by IQWIG, since the authority has not considered the assessment as being mandatory, approved without restrictions in relation with the SmPC	15	Not to exceed 15 points	
2.5. New INNs, reimbursable INNs with extension of indication, for which the assessment report of the authorities for assessment of medical technologies of Germany (IQWIG/G-BA) demonstrates an additional therapeutic benefit as opposed to the comparator (regardless of its size), with restrictions in relation with the SmPC, and which are included into the GBA therapeutic guidelines and which have not been assessed by IQWIG since the authority has not considered the assessment as being mandatory, with restrictions in relation with the SmPC	7		
2.6. New INNs, reimbursable INNs with extension of indication for which the evaluation report of the authorities for assessment of medical technologies in Germany (IQWIG / G-BA) does not demonstrate additional therapeutic benefit as opposed to the comparator or the benefit is less as opposed to the comparator or for which no evaluation report has been issued	0		
3. Status of INN reimbursement in Member States/Positive assessment report from the National Agency for Medicines and Medical Devices of Romania			
3.1. New INNs, reimbursable INNs with extension of indication, for which inclusion into the List of the new therapeutic indication is required, reimbursed in at least 14 Member States and Great Britain	25	Not to exceed 25 points	

3.2. New INNs, reimbursable INNs with extension of indication, reimbursed in 8-13 Member States and Great Britain	20		
3.3. New INNs, reimbursable INNs with extension of indication, reimbursed in 3-7 Member States and Great Britain	10		
3.4. New INNs, reimbursable INNs with extension of indication in less than 3 Member States and Great Britain	0		
3.5. New INNs, reimbursable INNs with extension of indication or fixed-dose combinations of already reimbursable INNs, for which the applicant submits the following documents: (i) a clinical trial authorisation and an intermediate/final report validating the conduct in Romania of a clinical trial of the medicinal product assessed for the submitted indication; (ii) A EUnetHTA assessment for the submitted indication; (iii) proof of notification to the NAMMDR of a non-interventional study for the collection of real data for the submitted indication.	45	Not to exceed 45 points. **)	
4. Therapy costs			
4.1. New INNs, reimbursable INNs with extension of indication, generating more than 5% savings as opposed to the comparator, per patient, within the timeframe used for calculation	30	Not to exceed 30 points	
4.2. New INNs, reimbursable INNs with extension of indication, with a neutral budgetary impact as opposed to the comparator, per patient, within the timeframe used for calculation, generating between 5% savings and up to 3% costs)	15		
4.3. New INNs, reimbursable INNs with extension of indication, generating more than 3% costs as opposed to the comparator, per patient, within the timeframe used for calculation	0		

NOTE:

1. For indications for which a medicinal product corresponding to some new INNs, reimbursable INNs with extension of indication, the marketing authorisation for the evaluated medicinal product was issued before 2011 and the medicinal product is reimbursed in the United Kingdom and Germany, 15 points are awarded ex officio on criterion 2 of the table for both NICE and IQWIG / G-BA.

2. For fixed dose combinations whose components have already been included in the List, only the cost-minimisation analysis shall be provided, comparing costs/

recommended daily dosage (annual RDDs) with costs/annual RDDs, separately for the components of the combination. The combination shall only be included in the List for costs/annual RDDs lower or no higher than the summated costs/annual RDDs of the separate components. (In case of a double combination, the separate components should appear as reimbursed in the List, however one of the separate components should be reimbursed for the indication for which a fixed combination is submitted; in case of a triple combination, three separate components reimbursed in the List or a combination of one + double combination can be chosen, however both should be reimbursed in the List and it is mandatory that at least one of the separate components or the double combination be reimbursed for the indication for which a fixed combination is submitted).

3. The phrase "without restrictions on the summary of product characteristics" in criterion 2.4 means that all population subgroups have been allocated an additional therapeutic benefit regardless of its size (major, considerable, minor and non-quantifiable).

4. The phrase "with restrictions on the summary of product characteristics" under criterion 2.5 means that at least one population subgroup has not been allocated an additional therapeutic benefit.

5. The 45 points awarded in point 3.5 replace the score given for the reports of the medical technology assessment authorities of France (HAS), Great Britain (NICE / SMC) and Germany (IQWIG / G-BA) described under points 1 and 2 of Table 4.

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*) Cost / recommended daily dose (annual DDD) - the total price of the INN calculated at the level of the maximum retail price with WATT, Cost / recommended daily dose (annual DDD) present in the Index of Prices of Medicinal Products for Human Use approved on the date of evaluation, depending on the doses and duration of administration provided in the SmPC, for a calendar year. The cost / recommended daily dose (annual DDD) is for the same strength, pharmaceutical form or route of administration of INN and, if both the innovative medicinal product and the generic / biosimilar components of the fixed combination are available on the market, the amount of annual costs / DDD of the components taken separately is made at the level of generic / biosimilar medicinal products with the lowest maximum retail prices with VAT present in the Index of prices of medicinal products for human use, approved at the date of evaluation.

**) Considering the heterogeneity of non-interventional studies on pathologies, patient population, objectives pursued, type of data collected, analysis and interpretation of results, it is almost impossible to develop a unitary methodology for all types of non-interventional studies. The protocols submitted by the applicants will be analysed by the Health Technology Assessment Department and the Clinical Trials Department of the National Agency for Medicines and Medical Devices of Romania. The National Agency for Medicines and Medical Devices of Romania may invite representatives of the National Health Insurance House and of the advisory commissions of the Ministry of Health for consultations. Their main objectives will be the evaluation of the additional clinical benefit, of the safety, of the quality of life, namely the collection of direct costs from the payer's perspective in order to perform

pharmaco-economic analyses at the end of the study. The purpose of the working group is to analyse the design of the non-interventional study and to guide the applicant to a protocol for collecting real data from therapeutic practice in order to assess medical technologies. Non-interventional studies will have to comply with regulations of the Decision of the Scientific Council of the National Agency for Medicines and Medical Devices no. 6/2014 on authorisation by the National Agency for Medicines and Medical Devices of clinical trials / notification to the National Agency of Medicines and Medical Devices of non-interventional studies performed with medicinal products for human use in Romania, supplemented by Decision of the Scientific Council of the National Agency for Medicines and Medical Devices no. 25/2015. The maximum term in which the final opinion on the data collection protocol will be issued is 3 months from the date of submission of the study request by the applicant. The non-interventional study for collection of actual data will be conducted after inclusion of the medicinal product included in the study in the reimbursement system. "

11. In Annex 1, a new Table is introduced after Table 4, namely Table 41, which reads as follows:

"Table 41 - Assessment criteria for generics or biosimilars without reimbursable INNs in the List

Assessment criteria	Rating	A single rating selected	Scores may be summated.
1. HTA based on estimation of the therapeutic benefit (SMR)			
1.1. Generics without reimbursable INNs in the List, biosimilars with no reimbursable INN in the List, which have received the BT-1 classification - major/important from HAS, for the INN	15	Not to exceed 15 points	
1.2. Generics without reimbursable INNs in the List, biosimilars with no reimbursable INN in the List, which have received the BT-2 classification - moderate/low (but which justifies reimbursement) from HAS, for the INN	7		
1.3. Generics with no reimbursable INN in the List, biosimilars with no reimbursable INN in the List, which have received the BT-3 classification - insufficient according to HAS	0		
2. HTA based on cost-efficacy			
2.1. Generics without reimbursable INNs in the List, biosimilars with no reimbursable INN in the List, which have received a positive opinion, approved without restrictions in relation with the SmPC, by Great Britain authorities for assessment of health technologies (NICE/SMC), for the INN, or for which	15	Not to exceed 15 points	

the MAH/MAH representative submits an affidavit attesting free of restriction reimbursement in Great Britain, with restrictions compared with the SmPC, also following a NICE class assessment or assessment of other types of reports/reviews performed by the NHS and related documentation			
2.2. Generics without reimbursable INNs in the List, biosimilars with no reimbursable INN in the List, which have received a positive opinion, with restrictions in relation with the SmPC, from the Great Britain authority for assessment of health technologies (NICE/SMC), for the INN, or for which the MAH/MAH representative submits an affidavit attesting free of restriction reimbursement in Great Britain, with restrictions compared with the SmPC, also following a NICE class assessment or assessment of other types of reports/reviews performed by the NHS and related documentation	7		
2.3. Generics without reimbursable INNs in the List, biosimilars with no reimbursable INN in the List, which (i) have received a negative opinion from the Great Britain authority for assessment of health technologies (NICE or SMC) or (ii) for which no assessment report has been issued and for which the MAH/MAH representative has not issued an affidavit related to the reimbursement status in Great Britain	0		
2.4. Generics with no reimbursable INN in the List, biosimilars with no reimbursable INN in the List, for which the assessment report of the authorities for assessment of medical technologies of Germany (IQWIG/G-BA) demonstrates an additional therapeutic benefit as opposed to the comparator (regardless of its size), approved without restrictions in relation with the SmPC and which are included into the GBA therapeutic guidelines and have not been assessed by the IQWIG since the authority has not considered the assessment as being mandatory, approved without restrictions in relation with the SmPC	15	Not to exceed 15 points	
2.5. Generics without reimbursable INNs in the List, biosimilars with no reimbursable INN in the List, for which the assessment report of the authorities for assessment of medical technologies of Germany (IQWIG/G-BA) demonstrates an additional	7		

therapeutic benefit as opposed to the comparator (regardless of its size), with restrictions in relation with the SmPC and which are included into the GBA therapeutic guidelines and have not been assessed by the IQWIG since the authority has not considered the assessment as being mandatory, with restrictions in relation with the SmPC			
2.6. Generics without reimbursable INNs in the List, biosimilars without reimbursable INNs in the List, biosimilars with no reimbursable INN in the List, for which the assessment report of the authorities for assessment of medical technologies of Germany (IQWIG/G-BA) does not demonstrate an additional therapeutic benefit as opposed to the comparator or the benefit is smaller as opposed to the comparator or for which an assessment report has not been issued by the authorities for assessment of medical technologies of Germany (IQWIG/G-BA)	0		
3. The reimbursement status of the INN in EU Member States and Great Britain/positive assessment report issued by the National Agency for Medicines and Medical Devices of Romania			
3.1. Generics without reimbursable INNs in the List, biosimilars with no reimbursable INN in the List, requiring inclusion of the new therapeutic indication in the List reimbursed in at least 14 of the EU Member States and Great Britain	25	Not to exceed 25 points.	
3.2. Generics without reimbursable INNs in the List, biosimilars with no reimbursable INN in the List, reimbursed in 8 - 13 EU member states and Great Britain	20		
3.3. Generics without reimbursable INNs in the List, biosimilars with no reimbursable INN in the List, reimbursed in 3 - 7 EU member states and Great Britain	10		
3.4. Generics without reimbursable INNs in the List, biosimilars with no reimbursable INN in the List, reimbursed in less than 3 EU member states and Great Britain	0		
4. Therapy costs			
4.1. Generics or biosimilars with no reimbursable INN in the List, generating more than 30% savings as opposed to the comparator*), for generics, and more than 15% as opposed to the comparator*), for biologicals, per patient, per year	30	Not to exceed 30 points.	

4.2. Generics or biosimilars with no reimbursable INN in the List, generating between 30% savings and up to 3% costs as opposed to the comparator*), for generics, and between 15% savings and up to 3% costs as opposed to the comparator*), for biologicals, per patient, per year	15		
4.3. Generics or biosimilars with no reimbursable INN in the List, generating more than 3% costs as opposed to the comparator*), per patient, per year	0		

NOTE:

1. The phrase « without restrictions on the summary of product characteristics» under criterion 2.4 refers to the fact that an additional therapeutic benefit was allocated to all population subgroups regardless of its size (major, considerable, minor and non-quantifiable).

2. The phrase «with restrictions on the summary of product characteristics» under criterion 2.5 refers to the fact that no additional therapeutic benefit was allocated to at least one population subgroup.

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*) By way of exception, in case of generics and biosimilar products that do not have a reimbursed INN in the List, the comparator will be the innovative / biological drug for the same concentration, pharmaceutical form or route of administration. The maximum price levels for the innovative or biological medicinal product will be established by the Ministry of Health, at the request of the National Agency for Medicines and Medical Devices of Romania, according to the rules for calculation of the maximum prices of medicinal products for human use approved by Minister Order for the month in which the application for assessment is submitted, and will be sent within maximum 30 days from the date of application. The maximum price levels for the innovative or biological medicinal product will be specified in the assessment report for the generic / biosimilar medicinal product.

NOTE: for indications for which a generic or biosimilar medicinal product that does not have a reimbursed INN in the List, the MAH has submitted the documentation for assessment of health technologies in Table 41, and the marketing authorisation of the innovative or biological reference medicinal product related to the assessed INN was issued before 2011 and is reimbursed in the United Kingdom and Germany, 15 points are awarded ex officio according to criterion no. 2 in the Table for both NICE and IQWIG / G-BA."

12. In Annex 1, Table 5 is amended and shall read as follows:

"Table 5. - Assessment criteria for new INNs approved by the European Medicines Agency as orphan medicinal products or medicinal products for advanced therapy

Criterion	Points

1. Treatment, prevention or diagnosis of diseases that do not affect more than 5 in 10.000 people in the EU or are life-threatening, are chronically debilitating or represent serious and chronic diseases of the body. In addition, there is no satisfactory method of diagnosis, prevention or treatment authorized in the EU for these diseases or, if such method exists, the medicinal product brings a significant benefit to those suffering from this disease or new INNs approved for advanced therapy medicinal products.	70
2. The applicant shall provide one of the following documents for the orphan medicinal product or the advanced therapy medicinal product: a) A clinical trial authorisation and an intermediate/final report validating the conduct in Romania of a clinical trial of the medicinal product assessed for the submitted indication; b) A EUnetHTA assessment for the submitted indication; c) An authorisation for use in last resort treatments in Romania for the medicinal product assessed for the submitted indication; d) The approval for donation released by the NAMMDR and the evidence of treatment with the donated medicinal product for a period of at least 12 months, for the submitted indication, for a proportion of at least 50% of the population eligible for treatment, according to the SmPC.	10
NOTE: The MAH may submit to the assessment dossier an estimate of the eligible population corresponding to the indication of the orphan medicinal product/advanced therapy medicinal product, indicating the sources of the submitted data. "	

13. In Annex 1, a new table is introduced after Table 5, namely Table 51, which reads as follows:

"Table 51 - Criteria for assessment of newly approved INNs for the treatment of infectious diseases caused by pathogens that may cause epidemics / pandemics with a major impact on public health	
Criterion	Points
New INN approved for the treatment of infectious epidemic diseases	80"

14. In Annex 1, Table 7 is amended and shall read as follows:

"Table 7 - Criteria for assessment of new INNs for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative and for which there is no relevant comparator in the List

Assessment criteria	Rating	A single rating selected	Scores may be summated
1. HTA based on therapeutic benefit estimate (SMR)			
1.1. New INNs, reimbursable INNs with extension of indication, for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative, which have received the classification BT 1 - major/important from HAS	15	Not to exceed 15 points	
1.2. New INNs, reimbursable INNs with extension of indication for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative, which have received the classification BT 2 - moderate/low (but which justifies reimbursement) from HAS	7		
1.3. New INNs, reimbursable INNs with extension of indication for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative, which have received the classification BT 3 - insufficient according to HAS	0		
2. HTA based on cost-efficacy			
2.1. New INNs, reimbursable INNs with extension of indication, for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative, which have received a positive opinion, approved without restrictions in relation with the SmPC, by Great Britain authorities for assessment of health technologies (NICE/SMC) or for which the MAH/MAH representative submits an affidavit attesting free of restriction reimbursement in Great Britain, with restrictions compared with the SmPC, also following a NICE class assessment or assessment of other types of reports/reviews performed by the NHS and related documentation	15	Not to exceed 15 points	
2.2. New INNs, reimbursable INNs with extension of indication, for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative, which have received a positive opinion, with restrictions in relation with the SmPC, from authorities for assessment of health technologies in Great Britain (NICE/SMC) or for	7		

which the MAH/MAH representative submits an affidavit attesting free of restriction reimbursement in Great Britain, with restrictions compared with the SmPC, also following a NICE class assessment or assessment of other types of reports/reviews performed by the NHS and related documentation			
2.3. New INNs, reimbursable INNs with extension of indication for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative, which have received a negative opinion from the Great Britain authority for assessment of health technologies (NICE/SMC) or which have not received a report	0		
2.4. New INNs, reimbursable INNs with extension of indication for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative, for which the assessment report of the authorities for assessment of medical technologies of Germany (IQWIG/G-BA) demonstrates an additional therapeutic benefit as opposed to the comparator (regardless of its size), approved without restrictions in relation with the SmPC, and which are included into the GBA therapeutic guidelines and have not been assessed by the IQWIG since the authority has not considered the assessment as being mandatory, approved without restrictions in relation with the SmPC	15	Not to exceed 15 points	
2.5. New INNs, reimbursable INNs with extension of indication, for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative, for which the assessment report of the authorities for assessment of medical technologies of Germany (IQWIG/G-BA) demonstrates an additional therapeutic benefit as opposed to the comparator (regardless of its size), with restrictions in relation with the SmPC, and which are included into the GBA therapeutic guidelines and have not been assessed by the IQWIG since the authority has not considered the assessment as being mandatory, with restrictions in relation with the SmPC	7		
2.6. New INNs, reimbursable INNs with extension of indication for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative, for which the	0		

assessment report of the authorities for assessment of medical technologies of Germany (IQWIG/G-BA) did not demonstrate an additional therapeutic benefit as opposed to the comparator or the benefit is smaller as opposed to the comparator or for which an assessment report has not been issued			
3. The INN reimbursement status in EU Member States and the United Kingdom / Positive Assessment Report issued by the National Agency for Medicines and Medical Devices (NAMMDR)			
3.1. New INNs, reimbursable INNs with extension of indication, for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative reimbursed in at least 14 member states of the EU and great Britain	25	Not to exceed 25 points.	
3.2. New INNs, reimbursable INNs with extension of indication, for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative reimbursed in 8 - 13 member states of the EU and great Britain	20		
3.3. New INNs, reimbursable INNs with extension of indication, for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative reimbursed in 3 - 7 member states of the EU and great Britain	10		
3.4. New INNs, reimbursable INNs with extension of indication, for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative reimbursed in less than 3 member states of the EU and great Britain	0		
3.5. New INNs, reimbursable INNs with extension of indication, for which the applicant submits at least one of the following documents: (i) A clinical trial authorisation and an intermediate/final report validating the conduct in Romania of a clinical trial of the medicinal product assessed for the submitted indication; (ii) A EUnetHTA assessment for the submitted indication; (iii) Proof of notification to the NAMMDR of a non-interventional study for the collection of real data for the submitted indication.	45	Not to exceed 45 points.*)	
4. Evolutionary stage of the pathology			
4.1. New INNs, reimbursable INNs with extension of indication, for the treatment of rare diseases or for	10		

evolutionary stages of some pathologies for which the INN is the only therapeutic alternative in patients with an average life expectancy of less than 24 months / paediatric patients aged 0 to 12 months		Not to exceed 30 points.	
4.2. New INNs, reimbursable INNs with extension of indication, for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative, for which the treatment: a) increases the average survival by at least 3 months; or b) causes the remission to be maintained or to stop / slow down the evolution of the disease to the advanced stages of severity, for a period longer than 3 months	10		
4.3. New INNs, reimbursable INNs with extension of indication, for the treatment of rare diseases that do not affect more than 5 in 10.000 people in the EU or are life-threatening, are chronically debilitating or represent serious and chronic diseases of the body, according to information provided on the OrphaNet website or statistics from European countries / local statistics	10		

*) The 45 points substitute the rating granted for the reports of the authorities for assessment of medical technologies of France (HAS), Great Britain (NICE/SMC) and Germany (IQWIG/G-BA) described under points 1 and 2 of the Table.

NOTE:

1. For the indications for which a medicinal product corresponding to new INNs, reimbursable INNs with extension of indication, for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative, the documentation for the assessment of medical technologies was submitted in Table 7, and the marketing authorisation for the assessed medicinal product was issued before 2011 and the medicinal product is reimbursed in the United Kingdom and Germany, 15 points are granted ex officio, according to criterion no. 2 from the Table for both NICE and IQWIG/G-BA.

2. The phrase « without restrictions on the summary of product characteristics» under criterion 2.4 refers to the fact that an additional therapeutic benefit was allocated to all population subgroups regardless of its size (major, considerable, minor and unquantifiable).

3. The phrase «with restrictions on the summary of product characteristics» under criterion 2.5 refers to the fact that no additional therapeutic benefit was allocated to at least one population subgroup.

4. Given the heterogeneity of non-interventional studies on pathologies, patient population, the objectives pursued, the type of collected data, analysis and interpretation of results, it is almost impossible to develop a unitary methodology for all types of non-interventional studies. The protocols submitted by applicants

will be analysed by the NAMMDR, which may invite representatives of the National Health Insurance House and the specialized commissions of the Ministry of Health for consultation on: assessment of the additional clinical benefit, safety, quality of life and collection of direct costs from the payer's perspective in order to perform pharmaco-economic analyses at the end of the study, in order to guide the applicant for the collection of real data from therapeutic practice, in order to evaluate medical technologies. The non-interventional study for the collection of real data will be carried out after inclusion of the medicinal product included in the study in the reimbursement system.

5. The criteria for issuance of a decision to include, extend indications or not include medicinal products approved by the European Medicines Agency as orphan medicinal products or medicinal products for treatment of rare diseases or for developmental stages of certain pathologies for which the respective INN is the only therapeutic alternative are the same as provided in section I letter B points 1 and 2 of Annex 2 to the Order."

15. In Annex 1, a new Table is introduced after Table 8, namely Table 9, which reads as follows:

"Table 9 - Assessment criteria for medicinal products corresponding to a reimbursed INN in the List, with a decision for conditional inclusion, with an ongoing cost-volume / cost-volume-result contract, which have cumulatively lost data exclusivity and no longer benefit from patent protection and / or certificates for additional protection and its generic(s), namely whose biosimilar meets the marketing conditions on the Romanian territory

Criterion		Points
1. Estimate of the budgetary impact		
1.1. Generics who have a reimbursed INN in the List with decision for conditional inclusion, biosimilars who have a reimbursed INN in the List, with decisions for conditional inclusion, generating more than 30% savings compared to the medicinal product in cost-volume / cost-volume-result for the generic, namely more than 15% savings for the biosimilar, per patient, per year	30	Not to exceed 30 points
1.2. Generics that have the INN reimbursed in the List, with decision for conditional inclusion, biosimilars who have a reimbursed INN in the List, with decisions for conditional inclusion, that generate less than 30% savings compared to the medicinal product in cost-volume / cost-volume-result for the generic, namely less than 15% savings for the biosimilar, per patient, per year	0	
2. The rating obtained by the INN reimbursed in the List on the decision of conditional inclusion in the List, based on which a cost-volume / cost-volume-result contract was concluded		
NOTE:		

The assessment is performed by the NAMMDR upon notification by the Ministry of Health or the National Health Insurance House or upon notification of a marketing authorisation holder for a generic/biosimilar medicinal product reimbursed in the List, with a decision of conditional inclusion."

16. In Annex 2 section I, preamble of letter A is amended and shall read as follows:

"A. Stages of the medicinal product assessment process for new INNs for inclusion in the List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programmes, hereinafter referred to as the List, and of medicinal products corresponding to the INNs reimbursed for the extension of the indications or addition according to the criteria provided in Art. 1 n) of Annex 1 to the Order, generic medicinal products or biosimilars without reimbursable INNs in the List, orphan medicinal products, advanced therapy medicinal products, medicinal products corresponding to new INNs for the treatment of rare diseases or for evolutionary stages of some pathologies for which the INN is the only therapeutic alternative and for which there is no relevant comparator in the List of new plasma-derived INNs for the treatment of rare diseases for which the INN is the only therapeutic alternative ".

17. In Annex 2 section I point A, a new point is introduced after point 2, point 21, which reads as follows:

"21. For a reimbursed INN in the List, with a decision of conditional inclusion, with an ongoing cost-volume / cost-volume-result contract, whose cumulative reference medicinal product has lost its data exclusivity and no longer benefit from patent protection and / or certificates for additional protection and whose generic(s), namely its biosimilar(s), meet(s) the marketing conditions on the Romanian territory, the NAMMDR initiates the assessment process after receiving the request, prepared in line with the template provided in Annex 4 to the Order, by a MAH, for a generic / biosimilar, or as a result of its notification by the Ministry of Health or the National Health Insurance House. "

18. In Annex 2 section I point A, points 7, 9, 10, 18, 22 and 23 are amended and shall read as follows:

"7. The preliminary analysis of the assessment reports of the medical technologies submitted by the applicant, the analysis of the reimbursement evidence from European Union member states, the calculation and analysis of the therapy cost are performed by the National Agency for Medicines and Medical Devices of Romania (NAMMDR), within maximum 30 calendar days from submission of the documents.

.....

9. If the submitted documentation is incomplete or an irrelevant comparator for the medical practice in Romania was used to calculate the therapy cost, the National Agency for Medicines and Medical Devices of Romania sends to the applicant, within maximum 30 calendar days from submission of the documentation,

an information requesting submission of additional documentation or completion of the submitted documentation, as the case may be.

10. The information contains the critical analysis of the submitted documentation and the proposals for its amendment or supplementation, as the case may be, including the comparator considered relevant for medical practice in Romania, endorsed by the advisory commissions of the Ministry of Health.

.....

18. Requests and extended documentation received are analysed in order of priority, according to the following prioritization criteria:

1. medicinal products which have gone through a previous assessment process, concluded with a decision of non-inclusion, as a result of non-compliance with maximum of two criteria, the decision being uncontested or not modified as a result of solving the appeal, for which the MAH presents elements that meet a more favourable rating, according to this Annex;

2. medicinal products for diseases in evolutionary stages of the disease without a therapeutic alternative in the List;

3. medicinal products approved through emergency procedure by the European Medicines Agency;

4. medicinal products corresponding to INNs for specific treatment in case of diseases with a major impact on public health, provided in Law no. 95/2006 on healthcare reform, republished, as further amended and supplemented, as well as in the National Health Strategy;

5. the chronological order in which the assessment applications have been submitted, for medicinal products which do not fall within the criteria provided in subpoints 1 - 4.

As regards the situations provided in subpoints 1 – 4, the analysis will be performed on each situation in the chronological order in which the assessment applications have been submitted.

.....

22. Therapy costs are estimated according to the relevant comparator for medical practice in Romania. If the relevant comparator for medical practice in Romania is not found in the documentation submitted by the applicant, this fact shall be mentioned in the information prepared by the NAMMDR, together with the opinion of the advisory commissions of the Ministry of Health, granted in order to substantiate the choice of the relevant comparator.

23. Therapy costs are calculated by the applicant and are submitted together with the assessment documentation to the NAMMDR, based on the following data:

Table 1 - Data needed to calculate therapy costs			
	New INN, reimbursable INNs with extension of	New INN, reimbursable INNs with extension of	Comparator

	indication, generics or biosimilars without reimbursable INNs in the List	indication under the conditions of employment in a cost-volume / cost-volume mechanism - result	
The monthly therapy cost with the minimum daily dose			
The monthly therapy cost with the maximum daily dose			
The monthly cost of the recommended dose therapy			
The total number of patients for the respective indication (prevalence and incidence) estimated to be treated annually and estimates for a period of 5 years, after inclusion in the List			
Duration of therapy per patient, according to the SmPC, or median duration of treatment in the clinical trials on which the authorisation was based			

NOTE:

1. Therapy cost - the total price of INNs calculated at the maximum retail price level including VAT, present in the National Index of Prices of Medicinal Products for Human Use, approved on the date of assessment, depending on the doses and duration of administration provided in the SmPC, for a calendar year, per patient. The therapy cost is made on the recommended dose of the comparator which has the same approved indication and is addressed to the same population segment as the assessed medicinal product, and if the innovative medicinal product and the generics for the chosen comparator are both on the market, namely both the biological medicinal product and its biosimilar, the therapy cost is related to the generic / biosimilar medicinal product with the lowest maximum retail price with VAT present in the National Index of Prices of Medicinal Products for Human Use, approved at the date of assessment. If administration of an assessed therapeutic scheme in combination with other medicinal products related to reimbursed INNs is specified, in the SmPC, for the assessed INN or comparator, the therapy cost will be calculated for the entire therapeutic scheme. If in the SmPC, for the INN under evaluation or for the comparator, the recommended dose involves a period of induction of treatment and a period of its consolidation, the therapy cost per patient will be calculated for a period of three calendar years. If in the SmPC, for the INN under evaluation or for the comparator, the recommended dose for one of them

involves a limited period of administration, of several months/years, and for the other an unlimited period of chronic administration, the therapy cost per patient will be calculated for a period of five calendar years.

2. By waiver from point 1, in case the MAH/MAH representative expresses his availability to conclude a protocol with the National Health Insurance House (CNAS) for co-financing of the treatment, according to Art. 220 (2) and Art. 221 (1) m) of Law no. 95/2006 on healthcare reform, republished, as further amended and supplemented, the therapy cost will be calculated considering the cost resulting from the application of the conditions mentioned in the address of expression of availability. The expression of the availability to enter into a protocol with the NHIH will be submitted as part of the assessment dossier.

3. The therapy cost shall be calculated in accordance with point 1 and for medicinal products for which the addition criteria for a reimbursed INN, included in the List, based on the medical technologies assessment, apply.

4. In cases of addition of another strength or pharmaceutical form used for the same indication as the strength or pharmaceutical form already assessed, the comparator is the medicinal product with the strength or pharmaceutical form corresponding to the already reimbursed INN included in the List based on the assessment of medical technologies."

19. In Annex 2 section I point A, a new point is introduced after point 24, namely point 241, which reads as follows:

"241. The NAMMDR consults with the specialised commissions within the Ministry of Health and takes into account their opinions, in line with the legal provisions in force, in the following situations:

a) when the point of view of the NAMMDR differs from that of the marketing authorisation holder regarding the choice of the comparator;

b) in order to validate the eligible population, according to the document submitted by the MAH, for calculation of the budgetary impact;

c) for positioning the medicinal product in the therapeutic strategy.

The opinion of the specialised commission communicated to the NAMMDR will be accompanied by bibliographical references supporting the substantiation of the opinion."

20. Point b) of Annex 2 section I point B point 5 is amended and shall read as follows:

"b) Obtaining a rating between 30 and 49 points following assessment of medical technologies carried out under the conditions of this methodology leads to the transfer of the INN to another sublist; the new reimbursement level is established in accordance with the methodology provided in Art. 1 k) from Annex 1 to order".

21. In Annex 2 section I point B, point 6 is amended and shall read as follows:

"6. Criteria for issuing the decision for addition:

a) a medicinal product corresponding to an already reimbursed INN which, according to the SmPC, is addressed to another population segment for the indication for which it was included in the List based on the assessment of health technologies;

b) a medicinal product corresponding to an already reimbursed INN which, according to the SmPC, can be administered in other treatment lines for the indication for which it was included in the List based on the assessment of health technologies;

c) a medicinal product corresponding to an INN already reimbursed with strengths and / or other pharmaceutical forms than the strengths and / or pharmaceutical forms related to the indication for which it was included in the List based on the assessment of health technologies;

22. In Annex 2 section I point B, the introductory part of point 7 is amended and shall read as follows:

"7. Criteria for issuance of a decision for removal / addition of the ranking with (*), (**), (**) 1 or (**) 2:".

23. In Annex 2 section I point B, two new points are introduced after point 7, points 8 and 9, which read as follows:

"8. If, for the same indication mentioned in the SmPC, at the time of submission of the documentation for assessment, a medicinal product related to a new INN or corresponding to an expanded reimbursed INN for which the documentation was submitted for assessment in Table 4, 41 or Table 7 of Annex 1 to the Order, is administered in two or more treatment regimens or in two or more treatment lines on the same indication and the same population segment / subgroup, the decision of unconditional inclusion is issued only if the rating required for unconditional admission to the List is obtained, for all treatment regimens / lines. In the other cases, a conditional inclusion decision will be issued for all treatment regimens / treatment lines. In order to implement this methodology, treatment schemes/lines must be included simultaneously in the SmPC; if a new regimen / treatment line is added to the medicinal product for assessment after submission of the assessment documentation following approval of the European Medicines Agency after the initial MA has been obtained, it will be evaluated under the "addition" procedure.

9. If the comparator for a medicinal product with a new INN or reimbursable INNs with extension of indication, evaluated on Table 4 of Annex no. 1 to the Order, is a medicinal product corresponding to a reimbursed INN based on a cost-volume / cost-volume-result contract, a decision of conditional inclusion in the List is issued even if the rating obtained after assessment would allow unconditional inclusion in the List. "

24. In Annex 2 section II, a new point is introduced after point 3, namely point 31, which reads as follows:

"31. If the court orders by executory decision the obligation of the NAMMDR to resolve a request made by a petitioner to include a drug in the List, NAMMD will proceed with priority to analyse the application and issue a reasoned assessment report, which will be the basis of the decision, according to the template in Annex 6 to the Order. The decision is communicated to the petitioner within a maximum of 7 working days from its issuance. The applicant shall also be informed about the available means of appeal in line with the legislation in force and about the deadlines allowed for the exercise of means of appeal. "

25. In Annex 3 point 2, point d) is amended and shall read as follows:

"d) proof of reimbursement in the Member States of the European Union - the affidavit of the marketing authorisation holder in respect of the countries in which the medicinal product is reimbursed according to that indication;"

26. Annex 6 is amended and replaced with the Annex which is integral part of this Order.

27. Throughout the order, the phrase "National Agency for Medicines and Medical Devices" is replaced by the "National Agency for Medicines and Medical Devices of Romania", the phrase "Health Technologies Assessment Department" is replaced by "specialised structure with responsibilities in health technologies assessment", and the phrase" calendar" is replaced by "working".

Art. II - (1) In order to ensure adequate safeguard of patients' right to life, for applications submitted before entry into force of this Order which are not solved by issuing a decision on the inclusion, non-inclusion, addition, removal or exclusion of medicinal products in / from the List, if the provisions of this Order are more favourable, the marketing authorisation holder may choose by submitting a request to the National Agency for Medicines and Medical Devices of Romania (NAMMDR) to resolve the application according to the provisions of this Order.

(2) The application by which the marketing authorisation holder expresses his option according to paragraph (1) shall be submitted to the NAMMDR within maximum 10 days from entry into force of this Order, under the sanction of revocation, and shall be resolved according to the order of priority established by this Order.

Art. III - This Order shall be published in the Official Gazette of Romania, Part I

pp. Minister of Health,
Romică Andrei Baciu,
Secretary of State

Annex
(Annex 6 to Order no. 861/2014)

THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES OF ROMANIA

DECISION no. ….. /…..

On seeing Application no. …… submitted to the National Agency for Medicines and Medical Devices of Romania concerning the medicinal product …….. .,

Taking into account the Assessment report set out by the Department for Health Technologies Assessment of the National Agency for Medicines and Medical Devices pursuant to provisions of Order no 861/ 2014 on approval of criteria and methodology for assessment of health technologies, of documentation to be submitted by applicants, methodological means used in the assessment for inclusion, extension of indications, non-inclusion into or exclusion from the List of International Non-proprietary Names of on prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programs, as well as the means for appeal thereof, as further amended and supplemented,

based on Article 7 (4) of Law 144/2010 on reorganisation of the National Agency for Medicines and Medical Devices of Romania, as amended, and on amendment of certain regulatory documents,

the President of the National Agency for Medicines and Medical Devices of Romania hereby decides on:

1. - Unconditional inclusion
- Non-inclusion
- Exclusion
- Conditional inclusion
- Extension of indications
- Addition/Relocation of a reimbursable INN
- Ranking of a reimbursable INN as (*), (**)1 or (**)2 of the INN:…….
- elimination of the ranking of a reimbursed INN with (*), (**), (**)1, (**)2 of INN: .....,

Pharmaceutical form: ……

Strength: …….

For the indication: ……..in the proposed List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal

products provided in national health insurance programs, sublist with reimbursable level ..... .

2. This Decision shall be communicated to the Applicant, the minister of Health and the National Health Insurance House.

President of the National Agency for Medicines and Medical Devices

……

Processed by CL

C.J. DA

Order no. 1.418
of 7 August 2020

on amendment of the Annex to Order of the Minister of Health no. 487/2020 on approval of the protocol for treatment of the infection with the SARS-Cov-2 virus

Published in: the Official Gazette of Romania no. 719 din 10 august 2020

On seeing the Approval report of the General Directorate for Medical Assistance and Public Health Programmes of the Ministry of Health no. NT 6.722 of 7.08.2020,

taking into account provisions of Article 16 (1) g) of Law 95/2006 on healthcare reform, republished, as further amended and supplemented,

pursuant to Article 7 (4) of Government Decision No. 144/2010 on organisation and operation of the Ministry of Health, as further amended and supplemented,

the minister of health hereby issues the following Order:

Art. I – The Annex to Order of the Minister of Health no. 487/2020 on approval of the protocol for treatment of the infection with the SARS-Cov-2 virus, published in the Official Gazette of Romania, Part I, no. 242 of 24 March 2020, as further amended, is amended and replaced with the Annex which is integral part of this order.

Art. II - This Order shall be published in the Official Gazette of Romania, Part I

p.p. the Minister of Health,
Romică-Andrei Baciu,
Secretary of State

Annex
(Annex to Order no. 487/2020)

PROTOCOL
on approval of the protocol for treatment of the infection with the SARS-Cov-2 virus

Taking into account the increase in the number of COVID-19 cases in Romania, including severe forms of the disease, and the accumulation of new clinical data, The Infectious Diseases Commission of the Ministry of Health proposes a revised treatment protocol; the first variant was based on a draft of infectious disease specialists from Cluj. This protocol addresses the general situation of patients with COVID-19, without addressing particular situations in detail. In order to carry out this protocol, the provisions of the documents issued by the World Health Organisation (WHO) and the European Centre for Disease Prevention and Control (ECDC), of the therapeutic guidelines elaborated in China, Italy, Belgium, USA (1 – 6) and other materials published since setup of the previous version were analysed.

Through the recommendations on the care of patients with SARS-CoV-2 infection, this protocol represents a support for the decisions of the medicinal product policy commissions within health units regarding the "off-label" use of some potentially active medicinal products.

This therapeutic protocol includes principles grouped in the following sections:

1. Antiviral medication
2. Immunomodulatory medication, including convalescent plasma
3. Anticoagulant medicines
4. Antibiotics and other antiinfective medicinal products (apart from COVID-19 medicinal products)
5. Support of vital functions
6. Other therapeutic measures

1. Antiviral medication

The evolution of COVID-19 has an initial phase dominated by viral replication, with a variable duration; during this time, the patient goes through a presymptomatic period in order to become symptomatic. Antiviral medication should be administered as soon as possible after diagnosis (preferably from the beginning of the symptomatic period), aiming at:

- limiting the risk of the patient's transition to the phase dominated by excessive inflammation, in which severe manifestations of disease occur more frequently;
- reducing the duration of the disease, shortening the patient's hospitalisation, which increases patient safety, thus reducing consumption of hospital care resources per patient.

People infected with SARS-CoV-2 who remain asymptomatic throughout the course of the infection do not receive treatment, as it has not been shown that this would reduce the duration of excretion of the virus.

Potentially active antivirals against SARS-CoV-2:

• (hydroxy)chloroquine

Hydroxychloroquine has demonstrated in vitro activity against SARS-CoV-2, as well as some positive results in the treatment of patients with COVID-19. Yao X and colleagues have discovered that, compared to chloroquine, hydroxychloroquine inhibits SARS-CoV-2 7.6 times more effectively in vitro. Hydroxychloroquine is better tolerated than chloroquine and has fewer medicinal product to medicinal product interactions; in addition, it has been widely used in long-term treatments in rheumatology, in even larger doses than those frequently used in the treatment of COVID-19 (600 mg/day compared to 400 mg/day), without generating significant side effects. (Hydroxy)chloroquine alters the pH of the cell membrane surface and thus inhibit the fusion of the virus to the cell membrane. Moreover, they can inhibit nucleic acid replication, glycosylation of viral proteins, virus assembly and virus release from the infected cell. Gautret C. et al. have evaluated 42 patients; a faster virus clearance in patients with COVID-19 who have received hydroxychloroquine has been observed (8). The balance of possible benefits/risks (in vitro efficacy, possible clinical efficacy and reduced risk of adverse effects) has placed hydroxychloroquine as an antiviral therapeutic alternative, also leading to an interim authorisation for use in the USA (9). Contradictory data on the clinical efficacy of hydroxychloroquine have subsequently emerged:

- inefficiency and adverse reactions: a randomized study of 150 patients showed no significant decrease in duration of SARS-CoV-2 negation and increased adverse reactions in patients treated with hydroxychloroquine (10), other studies showed that it did not reduce lethality, nor the need for intensive care (11, 12);

- Efficacy: A study of 2.541 patients in the United States showed a 66% reduction in the risk of COVID-19 death in patients with severe disease with hydroxychloroquine compared to the standard treatment: 13.5% versus 26.4% (13).

Three decisions had an important impact on the perception of the efficacy of hydroxychloroquine, namely:

- discontinuation of patient enrolment in the UK RECOVERY study in the hydroxychloroquine recipient group due to lack of efficacy in reducing mortality from COVID-19 (4 June 2020);

- suspension on 15 June 2020 of the provisional authorisation granted by the FDA for the use of hydroxychloroquine in the treatment of COVID-19;

- discontinuation of patients in the SOLIDARITY trial organised by the WHO, in the group of those receiving hydroxychloroquine, due to lack of efficacy in reducing mortality associated with COVID-19 (17 June 2020).

In Romania, hydroxychloroquine has been widely used for therapeutic purposes and sometimes in order to prevent the occurrence of severe forms of COVID-19; negative data and adverse effects have limited its prescription. However, given the existing favourable data, this medicinal product remains an alternative in the absence of more effective medicinal products.

A particularly debated issue is the association of hydroxychloroquine with azithromycin. Initial data suggested a significant enhancement of the clinical efficacy; subsequently, the published results did not find such a benefit. Co-administration of two medicinal products which can prolong QT pleads against this combination; two studies found a significant elongation of QT in more than 10% of patients treated with this combination (14, 15).

The situation of bacterial resistance in Romania is an additional counterargument to the use of azithromycin. The American Society of Infectious Diseases recommends the prudent use of (hydroxy)chloroquine and avoidance of the association between hydroxychloroquine and azithromycin (6).

• Protease inhibitors

Lopinavir is a protease inhibitor used to treat the HIV infection in combination with ritonavir in order to increase its availability. Lopinavir has some degree of activity against in vitro coronaviruses, SARS-CoV-2 included. The clinical data published to this date are inconsistent. Three observational studies failed to identify a reduction in the duration of virus excretion in patients treated with lopinavir / ritonavir compared to favipiravir or placebo (17 - 19), while the use of lopinavir / ritonavir resulted in faster elimination of the virus during the Wuhan epidemic, in the case of early administration, in the initial viral phase (20). In a randomized clinical trial on 200 patients with moderate to severe disease, Cao and colleagues have showed that lopinavir / ritonavir caused a faster regression of symptoms and reduced the death rate, with no difference in statistical significance; it should be noted that initiation of the viral treatment was relatively late in this study (21). In another single-blind trial (ELACOI Trial) performed on 44 patients with mild to moderate disease, lopinavir / ritonavir had more side effects and did not reduce the duration of viral excretion compared to umifenovir or placebo (22). Adverse reactions in patients in the study by Cao B. et al were discontinued in 14% of cases (21).

These outcomes have led to a decline in the use of lopinavir / ritonavir for the treatment of COVID-19. However, considering the existing favourable data, this medicinal product remains an alternative, in the absence of more effective products. An additional benefit is the liquid form of administration - usable in patients who received orotracheal intubation and in newborns.

Darunavir / Cobicistat and atazanavir / ritonavir have been used as alternatives for patients intolerant to lopinavir / ritonavir, but experience with these substances is much more limited (4,5); the darunavir / cobicistat manufacturer claims that this product is in vitro ineffective against SARS-CoV2 and discourages its use in patients with COVID-19 (23), therefore its use is no longer justified. Ritonavir in combination with darunavir has also been used as an alternative in patients not tolerating lopinavir / ritonavir, however, the experience is limited.

• Remdesivir

Remdesivir is another potentially useful antiviral for the treatment of COVID-19, which inhibits RNA-dependent RNA polymerase, prematurely blocking RNA transcription. It has in vitro activity against coronaviruses, including SARS-CoV-2 (25, 26). Data obtained in clinical trials in treatment of COVID-19 was

contradictory; Wang et al. included 237 patients in a comparative study on remdesivir versus placebo, which was prematurely discontinued due to lack of efficacy and an increased rate of side effects: 12% versus 5% placebo (27). Beigel J. et al., in another study involving 1063 severely ill patients treated with remdesivir versus placebo, there was a discrete benefit in terms of mortality: 8% versus 11.9% ($p = 0.06$) and duration until improvement: 11 days compared to 15 days, $p = 0.01$ (28). Goldman J.D. et al. showed a similar efficacy for the 5-day and 10-day treatment durations, namely (29).

It is currently used in clinical trials and can only be obtained for individual compassionate use for pregnant women or children over 12 years old with severe forms of COVID-19 (30); there is an "early access" programme in several countries of the European Unit, through which the national authority manages the use of remdesivir, based on a provisional registration of the product in Europe (31).

The current indication is harmonised with the general principle of the use of antivirals, as early as possible after the onset of symptoms, being more effective in patients with hypoxia who have not yet required mechanical ventilation or extracorporeal membrane oxygenation (6); the duration of administration became more flexible, 5 - 10 days (maximum duration for intubated patients), depending on the clinical evolution and the negation of SARS-CoV-2 PCR tests. The recommended doses are 200 mg on the first day (100 mg every 12 hours) and 100 mg in the following days, by intravenous infusion, after dilution in physiological serum; the duration of administration should be at least 30 minutes (31).

• Other potentially active antivirals

Umifenovir works against influenza viruses and is used in this indication in Russia and China; its antiviral action is based on blocking the penetration of the virus into the cells (fusion inhibitor) and on the immunomodulatory effect. One of its advantages consists of reduced adverse reactions. In the SARS-CoV-2 epidemics in China, umifenovir was used in combination with other antiviral medicinal products; Deng L. et al. found that, in patients with uncomplicated pneumonia in COVID-19, the association of umifenovir with lopinavir / ritonavir allowed faster nasopharyngeal clearance and a faster regression of pulmonary imaging changes compared to the regression in patients receiving lopinavir / ritonavir monotherapy (32). There are currently two ongoing clinical trials evaluating the effect of umifenovir compared to the effect of lopinavir / ritonavir, namely to the standard antiviral-free treatment. Umifenovir can also be used in children over 12 years of age for SARS-CoV-2 infection.

Given the favourable results reported and the low rate of adverse effects associated with its administration, umifenovir represents a solution; it should be used instead of another antiviral that is more difficult to tolerate (lopinavir / ritonavir, remdesivir or hydroxychloroquine).

Favipiravir is an RNA polymerase inhibitor that has been used for influenza and the Ebola infection. It was originally manufactured in Japan, but used more frequently in China; due to its teratogenic effects, its use is only allowed for special situations such as epidemics or emerging infections with influenza viruses, in Japan. As regards the SARS-CoV-2 infection, favipiravir was more efficient in terms of

viral eradication and regression of lung imaging than both lopinavir / ritonavir and umifenovir; (33, 34); the doses used were 1,600 mg every 12 hours on the first day, then 600 mg every 12 hours for 7-14 days. It is not indicated in children and has been used in China in patients of childbearing potential only if they had a negative pregnancy test and always associated with contraceptive medication during treatment and at least seven days after stopping it; men were advised to use a condom for at least one week after hospital discharge.

Given the selective inclusion criteria, the need to inform patients, the need for additional testing and the administration of contraceptives which may have significant interactions with other medicinal products, favipiravir remains a therapeutic alternative when other antivirals are not available and all conditions mentioned for safe administration are met - for example, in menopausal patients.

Table 1 - Antiviral medication proposed for the treatment of COVID-19

Medicinal product	Doses	Standard duration	Frequent adverse reactions
Hydroxychloroquine*)	2 x 400 mg/day on the first day (2 x 2 tbsp/day), then 2 x 200 mg/day (2 x 1 tbsp/day) Children: 5 mg/kgc/day in 2 doses	5 - 7 days	Rhythm / driving disorders
Lopinavir/Ritonavir**) ***)	2 x 400/ 100 mg/day Children: 2 x 300/75 mg/m2/day	7 - 14 days	Diarrhoea (40.9%), nausea (40.9%), stomatitis (18,2%), anaemia (45,0%), leukopenia (40.0%)
Umifenovir	3 x 200 (400) mg/day	10 days	
Favipiravir	1,600 mg every 12 hours on the first day, then 600 mg every 12 hours 1,800 mg every 12 hours on the first day, then 800 mg every 12 hours****)	10 days	Teratogenic#), hyperuricemia (5%)##), diarrhoea (4.8%)##)
Remdesivir	200 mg/ day on day 1 then 100 mg/day Children weighing less than 40 kg: 5 mg/kgc/day on day 1, then 2.5 mg/kgc/day	5 - 10 days	hepatic cytolysis, phlebitis, constipation, nausea

*) It is recommended to perform daily EKG for QT evaluation; Contraindications: QT> 500 msec; benefit-risk analysis for pregnant women.

**) No combination of lopinavir / ritonavir with hydroxychloroquine and / or azithromycin is used in patients with cardiac problems at risk for QT prolongation arrhythmias.

***) Lopinavir / ritonavir tablets lose about half of their effectiveness.

****) For these doses, the toxicity of favipiravir is not sufficiently studied.

#) To be used only with contraception in fertile patients and in patients of childbearing potential.

##) The rate of side effects comes from studies performed at lower doses than proposed.

To conclude, the antiviral treatment should be started as soon as possible after the onset of symptoms; Moderate-severe / critical forms will include two antivirals whenever possible, as there are no definite data on the high efficacy of any of the usable ones. The choice of antivirals will depend on the potential adverse reactions, the patient's pathologies, as well as the availability of one or another of the antivirals at a given time. The route of administration also influences the choice of antivirals - preferably remdesivir iv and / or lopinavir / ritonavir syrup for orotracheally intubated patients.

2. Immunomodulatory medication, including convalescent plasma

In some patients, the initial infectious phase is followed by a second stage, in which the inflammatory-immune response is exacerbated; clinically, this phase is associated with recrudescence / worsening of symptoms, particularly pulmonary ones; a significant proportion of the cases with unfavourable evolution is represented by patients with an excessive inflammatory response ("cytokine storm"), who are often adults without known previous pathologies. At the same time, another subgroup of patients may have a deficiency in immunity which prevents the control of the SARS-CoV-2 infection and predisposes to superinfections (patients in the classic risk groups are more common here). Extensive biological monitoring is important in order to seize the moment of the inflammatory reaction (excessive cytokine release), with the help of the C-reactive protein, blood count, blood test (lymphocytes, platelets), increased ferritin, increasing IL-6, increase in the fibrinogen and D-dimers level, increased LDH.

The administration of immunomodulatory medication seeks to reduce the risk of unfavourable evolution, including death, in these categories of patients. The expected beneficial effects can be counterbalanced by a too intense immunosuppression, with delayed eradication of the SARS-CoV2 infection and possible reactivation of chronic infections: tuberculosis, pneumocystosis, chronic viral hepatitis.

The main therapeutic essays for this purpose were based on: systemic corticosteroids, immunosuppressive medicinal products / modulators, convalescent plasma.

- Systemic corticosteroids

Corticosteroids are the main treatment for control of the excessive cytokine release syndrome. Used in patients with acute respiratory distress in COVID-19, corticosteroids significantly reduced lethality to 46% versus 62% in those who did not receive corticosteroids. An important argument in favour of their use was the preliminary data from the RECOVERY study; the 2,104 patients who received 6 mg of dexamethasone daily (until discharge or up to 10 days) had a significantly lower lethality rate: 22.9% compared to 25.7% among the other 4,321 patients; the benefit was found for various categories of hypoxic patients, but not for those who did not require additional oxygen (36).

Therefore, the specific indication is in cases of COVID-19 with excess inflammation (increased / increasing values of the monitored inflammation parameters, see above) and possibly with evolving pneumonia (polypnea, decrease of SpO2 below 93% and blood pressure of oxygen), when administration should be initiated as soon as possible: dexamethasone, iv, 8 - 24 mg / day, for 7 - 10 days, possibly methylprednisolone. The duration and dose are decided according to the patient's progress. Corticosteroids are not indicated in patients who maintain satisfactory respiratory function without additional oxygen supply, for whom the benefit is not obvious, but adverse reactions are as common as in other groups of patients (6).

The administration of corticosteroids is also justified in patients with COVID-19:

- in cases with other indication for use, such as asthma attack, exacerbated COPD or adrenal insufficiency;

- in cases of septic shock unresponsive to vasopressor amines (HHC, usually 50 mg every 6 hours).

Immunomodulators

• Tocilizumab

This IL-6 receptor antagonist has been used in a subgroup of patients with severe forms of COVID-19 with excessive inflammation activation ("cytokine storm"). Identification of patients who would benefit from tocilizumab can be based on parameters such as increased ferritin levels, decreased lymphocyte and platelet counts, increased C-reactive protein, fibrinogen, and D-dimer levels (37). There is data reported by Xu X et al. on efficacy of tocilizumab in a number of 21 Chinese patients; following administration of 1-2 doses of tocilizumab, afebrility, decreased oxygen demand and partial correction of lymphopenia were obtained in all patients (38). In an observational study of 154 patients with COVID-19 requiring mechanical ventilation, Somers E.C. and collaborators showed a 45% decrease in lethality, despite doubling of the risk of bacterial superinfection (54% vs. 26%) (39). Rojas-Marte G. and colleagues conducted a case-control study that included 193 patients with severe forms of COVID-19; a slightly lower lethality was observed in patients receiving tocilizumab (52% vs 62%), and the difference was significant in patients who did not receive mechanical ventilation, 6% vs 27% (40).

In the clinical experience of the authors, the results obtained with tocilizumab were favourable, following administration of 8 mg / kilogram body weight doses, repeated at 8 - 12 hours, up to a maximum of 3 administrations.

• Anakinra

Anakinra is an IL-1 receptor antagonist currently used in the treatment of rheumatoid arthritis and Still's disease; it is administered by subcutaneous route, 100 mg / day, but up to 400 mg / day can be administered in severe forms of inflammatory diseases. Off-label doses of up to 3,600 mg / day were used in the treatment of severe sepsis as a continuous infusion over several days without more frequent side effects compared to the standard doses. In the case of COVID-19, subcutaneous or intravenous use of 200-400 mg / day has been proposed for several days (up to 10 days). The first published data are favourable. Navarro-Millan I. and colleagues evaluated 11 patients who received anakinra in a New York hospital; the seven in whom treatment was initiated within the first 36 hours of respiratory failure did not reach mechanical ventilation, and of the other four patients, in whom the first dose was administered after more than four days of hypoxia, three survived (41). In another study in France, 25% of 52 patients treated with anakinra required intensive care, compared to 73% in a control group of 44 previously treated patients in the same hospital (42).

In the case of COVID-19, subcutaneous or intravenous use of 200-400 mg / day, in daily decreasing doses, was used for 7-10 days.

There were not sufficient results published for other immunomodulators: siltuximab (a series of 30 cases treated in Italy, with a better outcome than patients with standard treatment), baricitinib (a series of 12 patients with COVID-19 pneumonia, with clinical improvements in all patients), sarilumab (study discontinued prematurely due to lack of efficacy), rituximab.

Convalescent plasma

Convalescent plasma administration assumes that the former immunocompetent patient after the SARS-CoV-2 infection will have sufficient levels of protective antibodies to be used to limit viral replication and mitigate the excessive inflammatory response in a patient with COVID-19. Duan K. et al reported that clinical and biological improvement was observed in a series of 10 patients with COVID-19 with respiratory impairment who required additional oxygen and received convalescent plasma along with standard therapy at that hospital (43). Li L. et al conducted a randomized study of 103 patients that showed both a reduction in lethality and a higher rate of clinical improvement at 28 days, without reaching statistically significant differences compared to patients who did not received convalescent plasma (44).

In order to use convalescent plasma you need:

- to obtain the donor's consent after confirmation of his healing;

- the presence of sufficient anti-SARS-CoV-2 antibodies; the FDA recommends a neutralizing antibody titer of at least 1/160; since the determination of neutralizing antibodies is often not available, the IgG antibody titer is determined

by ELISA; a titer of more than 1/1350 correlates in more than 80% of situations with a sufficient titer of neutralizing antibodies (45);

- donor testing to meet blood donation criteria: the absence of blood-borne infections and the absence of anti-HLA antibodies which increase the risk of TRALI (transfusion related acute lung injury).

The occurrence of TRALI in a patient with severe COVID-19 may significantly worsen the respiratory dysfunction of a patient who already has severe respiratory impairment; volume overloads have also been reported following plasma transfusion in patients with COVID-19. In a database of 5,000 patients who received convalescent plasma, 4 deaths and 21 other major accidents related to the administration were recorded in the first hours: TRALI, post-transfusion overload and allergic reactions (46).

As regards the use of convalescent plasma there are uncertainties related to:

- optimal timing of harvesting - given the limited data on antibody dynamics, including the rapid decrease in the anti-SARS-CoV-2 IgG titer, during the first 2-3 months after healing (47, 48);

- the quality of antibody detection tests;

- effective plasma dose; doses of 200-400 ml were used.

This therapeutic method should be used as early as possible in patients with potentially severe forms of COVID-19; As the availability of effective convalescent plasma is currently limited, we believe that this therapeutic method should be used primarily in patients with a deficient inflammatory-immune response profile, in whom immunosuppression is contraindicated. Currently, the administration of convalescent plasma is done in Romania in line with Order of the Minister of Health no. 654/2020 on approval of the Methodology for the collection, testing, processing, storage and distribution of plasma from the cured donor of COVID-19 from intensive care units (ICUs) and the monitored use for critical patients with COVID-19 from the ICUs, as further amended and supplemented.

Table 2 - Immunomodulatory medication proposed for the treatment of COVID-19

Medicinal product	Doses	Standard duration	Frequent adverse reactions
Dexamethasone (backup alternative - methylprednisolone)	8 - 16 mg iv/day (24 mg/day in obese patients)	7 - 10 days	Irritation of the digestive mucosa, diabetes imbalance
Tocilizumab	8 mg/ kg (maximum 800 mg per administration)	1 - 3 administrations every 8 - 12 hours	Reactivation of some infections: tuberculosis, chronic hepatitis (HBV), herpes infections, impaired liver function to hepatic impairment, intestinal perforation, hypercholesterolemia

Anakinra		7 - 10 days	Liver damage
Convalescent plasma	200 - 400 ml	Single administration	acute respiratory distress (TRALI), post-transfusion overload, allergic reactions
Undergoing assessment: siltuximab, baricitinib, rituximab			

In conclusion, immunomodulatory treatment is indicated for a subset of patients with potentially severe development and should be initiated as soon as possible after onset of the inflammatory phase, based on benefit/risk criteria depending on cytokine release, risk of infection and other associated adverse reactions. A rational therapeutic approach would include two steps: a) corticosteroids and/or immunomodulators for oral/subcutaneous administration and b) immunomodulators administered in intravenous bolus (such as tocilizumab) associated with corticosteroids. The treatment with convalescent plasma is currently recommended as a priority in patients with severe forms, possibly associated with COVID-19 infections and reduced inflammatory response, to compensate for the immune response deficiency. The choice of immunosuppressants will depend on the possible side effects and pathologies of the patient, as well as on the availability of one or another of the immunomodulators at a given time.

3. Anticoagulant medication

The administration of anticoagulants to the patient with COVID-19 has:

- a prophylactic purpose, to prevent the occurrence of major thrombotic events and microthrombosis, especially in the pulmonary circulation;
- a therapeutic purpose, in case of major thrombotic events.

The accumulated data show that in COVID-19 there is an obvious procoagulant condition, which can aggravate the patient's progression by exacerbating the respiratory dysfunction, both by microscopic lesions, "pulmonary intravascular coagulation" and by major pulmonary thromboembolism. Deep venous thrombosis, repeated thrombosis of vascular access lines, etc. have also been described. Cui S. et al. identified deep vein thrombosis in 20 of the 81 patients with severe pneumonia admitted to ICUs, and in 17 of them the level of D-dimers was more than three times the normal value. Of the 20 patients, eight died (49). Conversely, therapeutic administration of fractionated heparins resulted in reduced lethality in a group of 449 patients with severe forms of COVID-19 and / or elevated D-dimers (50). Limiting patient mobilization during hospitalization and altered water balance may increase this risk of thromboembolic events.

Evaluation of the level of D-dimers, fibrinogen, platelets is mandatory and can provide a benchmark for the evolution of the case and the duration of administration. The results of Thachil J. et al. are usually consistent: elevated levels of D-dimers and fibrinogenemia and thrombocytopenia correlated with the severity of the case; a level of D-dimers at the initial assessment, of more than four times the normal level, is considered a criterion of disease severity, regardless of the degree of respiratory dysfunction (51). Prolongation of PT, APTT, increase in D-dimers,

decrease in fibrinogen and platelets indicate progression to disseminated intravascular coagulation (DIC).

Recommendations are:

- no anticoagulants are indicated for asymptomatic SARS-CoV-2 infections;

- continuation of anticoagulant treatment by patients who have previously initiated treatment for other conditions; if there are drug interactions with the COVID-19 treatment, switch to therapeutic administration of low molecular weight heparin;

- prophylaxis of deep vein thrombosis for all symptomatic hospitalized patients with standard doses of fractionated heparin (most data being related to the benefit of enoxaparin, 40 mg / day in adults with normal body weight, adjusted for obese and patients with renal impairment); in case of contraindications for them (platelets below 25,000 / mmc, active haemorrhage) fondaparinux will be used - ISTH (International Society on Thrombosis and Haemostasis) recommendation – or, if unavailable, mechanical prophylaxis of deep vein thrombosis will be used (51)

- prophylaxis with high doses of heparin (fractionated or not), administered every 12 hours ("intermediate" doses), is preferred in several clinics in some patients with risk factors for deep thrombosis and more severe forms of COVID-19, e.g. for patients in intensive care or after discharge from intensive care (52), in those with the cytokine storm syndrome and significant increase in D-dimers and / or fibrinogen; unpublished data from China indicate a definite benefit if D-dimer values are more than six times the normal level (53);

- anticoagulant treatment for patients with deep vein thrombosis, repeated thrombosis of the vascular approach lines or pulmonary thromboembolism, with unfractionated or fractionated heparin;

- anticoagulant prophylaxis after discharge will be administered selectively to patients recovering from a severe form of COVID-19, especially in those over 40 years, immobilized, with a personal history of higher than normal levels of thrombotic pathology or D-dimer; the recommended duration is 7 to 14 days for enoxaparin and six weeks for rivaroxaban or betrixaban after discharge (54).

In addition, we believe that patients with worsening respiratory dysfunction should receive a therapeutic dose of anticoagulant until a computed tomography scan is performed to rule out pulmonary thromboembolic lesions; if this scan is not possible, the patient will be left with therapeutic doses of anticoagulant for the time necessary to correct the respiratory problem and normalize the D-dimers level.

The classification of patients in one or another of these indications is re-evaluated according to the clinical evolution and laboratory data.

Rescue therapy in case of failure of heparin administration in pulmonary thromboembolism exceeds the scope of this protocol.

In conclusion, prophylactic administration of anticoagulant or continuation of pre-existing anticoagulant therapy is indicated for all symptomatic patients with COVID-19 unless they have an absolute contraindication. The administration of high doses of anticoagulant (intermediate or even therapeutic) is done for standard indications, but also for patients with COVID-19 with worsening respiratory distress and / or with marked inflammatory syndrome ("cytokine storm").

4. Antibiotics and other anti-infectives (except for those specific to COVID-19)

The administration of antibiotics and anti-infectives in patients with COVID19 aims to:

- treat initial COVID-19 associated infections (such as bacterial pneumoniae);
- treat infections associated with medical care, more frequently respiratory infections, and with other localisations as well: of soft parts, systemic infections and septic shock, C. difficile infections;
- a special situation of infections is the reactivation of infections in patients receiving immunosuppressive treatment (tuberculosis, herpes infections, pneumocystosis etc.).

During the first period of evolution of the disease, the patient with COVID-19 may have concomitant bacterial infections, usually respiratory, increased or increasing serum procalcitonin, leucocytosis with neutrophilia, radiological appearance of alveolar lung opacity, D-dimers > 1 μg/ml (55). The risk of concomitant bacterial infections appears to be significantly lower than in patients with influenza. A bacteriological screening with testing for the presence in the urine of pneumococcal or Legionella antigens, serologies for atypical bacteria, blood cultures is useful. The antibiotics recommended in early installed pneumonia are those recommended for community forms: amoxicillin clavulanate 1.2 g i.v. every 8 hours + doxycycline 100 mg every 12 hours or moxifloxacin 400 mg / day (for pregnant women: ceftriaxone + azithromycin); the duration of administration will not exceed 5-7 days. Doxycycline has been assigned an additional favourable role as a possible IL-6 inhibitor (56). Fluoroquinolone and macrolides (azithromycin included) should be avoided in patients with rhythm or conduction disorders due to the risk of triggering such manifestations by lengthening the QT interval. Although some studies report the efficacy of azithromycin in combination with hydroxychloroquine, there is contrary data as well, thus the inclusion of this antibiotic in the standard treatment of COVID-19 and / or bacterial infections in conditions of frequent resistance of pneumococci and probably of Mycoplasma pneumoniae to macrolides cannot be supported in Romania (8, 57).

The occurrence of mechanical ventilation associated pneumonia was rare in patients with COVID-19, even though the mean duration of ventilation was approximately 3 weeks; in an analysis of 150 cases treated in Wuhan, bacterial superinfection was recorded in 1% of those who survived and in 16% of those who died. In case of pneumonia associated with mechanical ventilation, a treatment scheme adapted to the microbial circulation from the respective intensive care unit will be used (58). In a meta-analysis, Lippi M shows that serum procalcitonin levels above 0.5 ng/ml are correlated with an increased risk of adverse outcome (59).

Following administration of immunosuppressants to control excessive inflammation, the patient should be monitored for the risk of bacterial superinfections and the reactivation of latent infections; in order to be able to assess these risks as accurately as possible, we recommend, along with the medical history,

the collection and storage of a blood sample prior to the first administration of immunosuppressant, from which serological tests (HSV), Quantiferon TB-Gold and other tests can be performed.

In conclusion, the administration of anti-infective medication, other than that specific to COVID-19, should be done in a cautious and selective manner. The correct use of medical history, physical examination data, biological tests (procalcitonin and complete blood count), imaging examinations and microbiological tests (blood cultures, other examinations) may allow the identification of patients in need of antibiotics to resolve COVID-19-associated infectious problems. Given the relative rarity of infections associated with this syndrome, the current situation should have a favourable unintended consequence, namely limitation of the selection pressure of antibiotic-resistant microorganisms and restriction of the circulation of these microorganisms.

5. Support of vital functions

Care of patients with severe and critical forms of COVID-19 will be provided by intensive care physicians. Although several syndromes have been described in the months following the onset of the pandemic, which may jeopardize the prognosis of the patient with COVID-19 (haemodynamic dysfunction, acute renal failure, severe bacterial superinfections), the severe respiratory impairment remains the main life-threatening condition and, therefore, special attention should be paid to the monitoring of respiratory function in the COVID-19 patient. The decrease in O2 saturation to 92% in the atmospheric air in patients at rest, with no previous respiratory distress, requires rapid evaluation of arterial gasometry and the enrichment of inspired air with oxygen; additional measures to reduce hypoxemia are decided by the intensive care physician. The aim is to avoid aggravation of tissue hypoxia without resorting as much as possible to more invasive interventions such as mechanical ventilation with IoT or extracorporeal oxygenation. Among the possible methods of intervention, it should be noted that the non-invasive ventilation is a procedure that involves a high risk of aerosolization of SARS-CoV-2, particularly in the mask ventilation variant.

The elements of detail in this regard go beyond the scope of this therapeutic protocol.

6. Other therapeutic measures may be useful in most cases:

- fighting fever (acetaminophen), myalgias
- fighting insomnia;
- limiting anxiety in order to improve general condition - lorazepam;
- combating nausea, vomiting - metoclopramide, ondasetron, possibly dexamethasone;
- in patients with viscous respiratory secretions - fluidification of secretions can be resorted to by nebulisations with acetylcysteine and beta-mimetics;

- eschar prophylaxis in the immobilized / severe patient requires a change of position every two hours;

- prophylaxis of stress ulcer by gastric antisecretory medicinal products and enteral nutrition;

- there is a risk of potentiation of activity between statins and ritonavir-associated protease inhibitors; therefore it is recommended to limit the dose of atorvastatin to 20 mg / day;

- in forms with significant inflammation and/or hypoxemia in diabetic patients, the risk of ketoacidosis is higher and correction with fast-acting insulin is recommended;

- giving up on smoking.

Controversial or seemingly unnecessary therapeutic interventions

Although the need to replace ACE inhibitors and / or sartans in the treatment of patients diagnosed with COVID-19 was discussed, the European Society of Cardiology group issued, on 13 March 2020, a recommendation for these medicinal products to be maintained in treatment regimens; a similar recommendation was issued in the USA on 17 March 2020 by the American Cardiology Association (60, 61).

There is a reluctance to use NSAIDs in the treatment of COVID-19 that has been widely disseminated in France since March 2020, related to the inhibition of the beneficial effect of inflammation in cases of low-medium severity COVID-19. There is no clinical data to support this claim; however, it is reasonable to be careful about side effects such as those related to kidneys or the digestive mucosa. Patients receiving NSAIDs for various conditions may continue the treatment if there are no major drug interactions with the COVID-19 medication, with monitoring for potential adverse reactions.

The following are considered unnecessary or even harmful: intravenous immunoglobulins, volume recovery with colloidal solutions (debatable for albumin) (58).

Table 3 - Proposed treatment depending on the severity of the COVID-19 case

Form of disease (severity)	Recommended treatment	Recommended duration
Asymptomatic	No	-
Mild - acute upper respiratory tract infections (RTIs)	An available antiviral Recommended anticoagulant prophylaxis (mandatory for inpatients) if they do not have anticoagulant therapy already underway for other indications	7 days

Average Pneumonia without severity criteria	Antivirals (preferably two) should be administered as early as possible Potential anticoagulants - prophylaxis, intermediate doses or therapy Dexamethasone (or methylprednisolone) 7 - 10 days +/- other immunomodulators	Depends on the patient's progress
Severe[a)]/ Critical[b)]	Antivirals (questionable clinical role beyond 12 to 14 days from the onset of symptoms; the epidemiological indication is maintained) + therapeutic anticoagulant + dexamethasone (corticosteroid), 7 - 10 days + tocilizumab (in patients with excessive inflammation) *), possibly other immunomodulators **) +/- Convalescent plasma +/- antibiotics	Depends on the patient's progress

a) Severe = at least one of the following: respiratory rate ≥ 30/min. (≥ 40/min. in preschoolers); SaO2 ≤ 93%; PaO2/ FiO2 < 300; pulmonary infiltrates that increase by more than 50% in 24 to 48 hours.

b) Critical = at least one of the following: acute respiratory distress; sepsis; alteration of consciousness; Multiple organ dysfunction syndrome (MODS).

*) For tocilizumab 1 - 3 doses of 8 mg / kg every 8 to 12 hours.

**) In case of unavailability of tocilizumab or earlier initiation in the patient with significant increasing inflammation.

The duration of treatment is indicative, it can be prolonged or shortened according to the patient's progress, but without being reduced to less than 5 days (provided that no severe side effects occur). The patient is monitored clinically and biologically - biochemically daily, in case of patients with moderate-severe-critical forms; the repetition of imaging and biological tests is mandatory in an emergency, in case of clinical aggravation.

Testing for viral RNA in faeces is not justified on the basis of existing data.

This protocol is based on the following references: *)

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*) References are reproduced in facsimile.

1) Organization WH. Clinical management of severe acute respiratory infection (SARI) when COVID19 disease is suspected: interim guidance, 13 March 2020. https://apps.who.int/iris/handle/10665/331446.

2) European Centre for Disease Prevention and Control. Guidance for discharge and ending isolation in the context of widespread community transmission of COVID-19, 8 April 2020. Stockholm: ECDC; 2020

3) Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition), China National Health Commission; March 4, 2020

4) Interim clinical guidance for patients suspected of/confirmed with COVID-19 in Belgium, 19 mars 2020; Version 4. https://epidemio.wiv-isp.be/ID/Documents/Covid19/COVID-9_InterimGuidelines_Treatment_ENG.pdf

5) GiViTI COVID19 meeting 10.03.2020 - intensive care patients

6) IDSA guidelines on the treatment and management of patients with COVID-19 https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ (Accessed on 17 July 2020).

7) Yao X, Ye F, Zhang M et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Clinical Infectious Diseases, 2020 Mar 9. pii: ciaa237.

8) Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020; 105949. doi:10.1016/j.ijantimicag.2020.105949

9) https://www.fda.gov/media/136537/download (Accessed on 12.04.2020)

10) Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ. 2020;369:m1849. Published 2020 May 14. doi:10.1136/bmj.m1849

11) Borba MGS, Val FFA, Sampaio VS, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2) Infection: A Randomized Clinical Trial. JAMA Netw Open. 2020;3(4):e208857. doi:10.1001/jamanetworkopen.2020.8857

12) Magagnoli J, Narendran S, Pereira F et al. Outcomes of Hydroxychloroquine Usage in US Veterans Hospitalized with COVID19, Med (2020), https://doi.org/10.1016/j.medj.2020.06.001

13) Arshada S, Kilgoreb P, Chaudhry ZS. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Infec Dis, 2020, 97: 396-403.

14) Molina JM, Delaugerre C, Goff J, et al. No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection. Médecine et Maladies Infectieuses 2020.

15) Chorin E, Dai M, Shulman E, et al. The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin. medRxiv 2020.

16) Choy KT, Wong AYL, Kaewpreedee P et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Res. 2020 Jun; 178: 104786.

17) Yan D, Liu X-y, Zhu Y-n, et al. Factors associated with prolonged viral shedding and impact of Lopinavir/Ritonavir treatment in patients with SARS-CoV-2 infection. 2020 doi: 10.1101/2020.03.22.20040832

18) Hu L, Chen S, Fu Y, et al. Risk Factors Associated with Clinical Outcomes in 323 COVID-19 Patients in Wuhan, China. medRxiv 2020 doi: 10.1101/2020.03.25.20037721.

19) Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020;395:1054-62

20) Jin YH, Cai L, Cheng ZH et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia. Military Medical Research (2020) 7:4.

21) Cao B, Wang Y, Wen D et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19 N Engl J Med. 2020 Mar 18. doi: 10.1056/NEJMoa2001282.

22) Li Y, Xie Z, Lin W, et al. An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI). medRxiv 2020 doi: 10.1101/2020.03.19.20038984

23) https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus

24) Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. Travel Medicinal product and Infectious Disease. 2020 Mar 5: 101615

25) Sheahan TP, Sims AC, Leist SR et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020; 11: 222.

26) Wang M, Cao R, Zhang L et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020; 30: 269-271. doi: 10.1038/s41422-020-0282-0. Epub 2020 Feb 4.

27) Wang Y, Zhang D, Guanghua D et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet, published online on 29 April 2020, doi.org/10.1016/S0140- 6736(20)31022-9

28) https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advancedcovid-19

29) Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med 2020 May 27. doi: 10.1056/NEJMoa2015301

30) https://www.gilead.com/news-and-press/company-statements/gilead-sciences-statement-on-access-toremdesivir-outside-of-clinical-trials (accesat 12.04.2020)

31) https://www.ema.europa.eu/en/documents/product-information/veklury-epar-product-information_ro.pdf (Accessed on 18.07.2020)

32) Deng L, Li C, Zeng Q. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. Journal of Infection, https://doi.org/10.1016/j.jinf.2020.03.002

33) Cai Q, Yang M, Liu D et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering

https://doi.org/10.1016/j.eng.2020.03.007

34) Chang C, Huang J, Cheng Z et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv preprint doi: https://doi.org/10.1101/2020.03.17.20037432.

35) Wu C, Chen X, Cai Y et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020.

36) The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. NEJM. DOI: 10.1056/NEJMoa2021436

37) Mehta P, McAuley DF, Brown M et al. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet, online March 13, 2020. https://doi.org/10.1016/ S0140-6736(20)30628-0

38) Xu X, M Han, Li T et al. Effective Treatment of Severe COVID-19 Patients with tocilizumab. In press.

39) Somers EC, Eschenauer GA, Troost JP et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19, Clinical Infectious Diseases, ciaa954, https://doi.org/10.1093/cid/ciaa954

40) Rojas-Marte G, Khalid M, Mukhtar O et al. Outcomes in patients with severe COVID-19 disease treated with tocilizumab: a case–controlled study, QJM: An International Journal of Medicinal product,

hcaa206, https://doi.org/10.1093/qjmed/hcaa206

41) Navarro-Millán I, Sattui SE, Lakhanpal A et al. Use of Anakinra to Prevent Mechanical Ventilation in Severe COVID-19: A Case Series Arthritis Rheumatol. 2020;10.1002/Art.41422.

42). Huet T, Beaussier H, Voisin O et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol 2020; 2: e393–400

43) Duan K, Liu B, Li C et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A. 2020 Apr 6. doi: 10.1007032/pn3as5.270034116811117 082020

44) Li L, Zhang W, Hu Y, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial [published online ahead of print, 2020 Jun 3]. JAMA. 2020;e2010044.

45) Salazar E, Kuchipudi SV, Christensen PA, et al. Relationship between Anti-Spike Protein Antibody Titers and SARS-CoV-2 In Vitro Virus Neutralization in Convalescent Plasma. bioRxiv 2020.

46) Joyner M, Wright RS, Fairweather D et al. Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. J Clin Invest. 2020. https://doi.org/10.1172/JCI140200.

47) Du Z, Zhu F, Guo F, Yang B, Wang T. Detection of antibodies against SARS-CoV-2 in patients with COVID-19 J Med Virol. 2020 Apr 3. doi: 10.1002/jmv.25820.

48) Long, Q., Tang, X., Shi, Q. et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med (2020). https://doi.org/10.1038/s41591-020-0965-6

49) Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020. 10.1111/jth.14830.

50) Song JC, Wang G, Zhang W et al. Chinese expert consensus on diagnosis and treatment of coagulation dysfunction in COVID-19. Military Medical Research (2020) 7:19 https://doi.org/10.1186/s40779-020-00247-7

51) Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. published: 25 March 25, 2020 10.1111/jth.14810

52) Brigham and Womens Hospital – COVID19 Clinical Guidelines. Hematology. Accessed on 17 July 2020: https://covidprotocols.org/protocols/hematology/#)thrombotic-disease

53) Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020. 10.1111/jth.14817.

54) Spyropoulos AC, Lipardi C, Xu J et al. Modified IMPROVE VTE risk score and elevated D-Dimer identify a High Venous Thromboembolism Risk in Acutely Ill Medical Population for Extended Thromboprophylaxis. TH Open 2020; 4: e59-r65.

55) Ruan Q, Yang K, Wang W et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med, 2020, Mar 3. https://doi.org/10.1007/s00134-020- 05991-x

56) Conforti C, Giuffrida R, Zalaudek I, Di Meo N. Doxycycline, a widely used antibiotic in dermatology with a possible anti-inflammatory action against IL-6 in COVID-19 outbreak. Dermatologic Therapy, https://doi.org/10.1111/dth.13437

57) European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2018. Stockholm: ECDC; 2019.

58) Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Medicinal product. Accessed on https://www.esicm.org/ssc-covid19-guidelines/

59) Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A metaanalysis. Clinica Chimica Acta, 2020; 505: 190-191.

60) https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esccouncil-on-hypertension-on-ace-inhibitors-and-ang

61) Patients taking ACE-I medicinal products and ARBs who contract COVID-19 should continue treatment, unless otherwise advised by their physician. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. https://www.hfsa.org/patients-taking-ace-i-and-arbs-who-contract-covid-19-should-continue-treatment-unlessotherwise- advised-by-their-physician/

Medicinal product batches recalled during the 3rd quarter of 2020

No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/MAH	Batch	Grounds for recall	Proposed action	Date of recall
1	Ranitidina LPH 150 mg	film-coated tablets	150 mg	ranitidine	Labormed Pharma SA	all batches	voluntary recall from the market, at pharmacy level, as a precautionary measure, of all batches blocked from sale following the identification of nitrosamine impurities	Voluntary recall and destruction	28.07.2020
2	Binocrit 30000 IU/0.75 ml	solution for injection in pre-filled syringe	30000 IU/0.75 ml	epoetin alfa	Hexal Biotech Forschungs GmbH-Germany/Sandoz GmbH-Austria	1905270026	voluntary recall from the market, at pharmacy level, following out of specification results approved for parameter "Met(54)Ox"	Voluntary recall and destruction	05.08.2020
3	Depakine 57.64 mg/ml	syrup	57,64 mg/ml	sodium valproate	Unither Liquid Manufacturing FRANCE/ Sanofi Romania SRL	592, 595	voluntary recall from the market, at pharmacy level, as a precautionary measure, following registration of a quality complaint in Poland	Voluntary recall and destruction	10.08.2020
4	Orfiril Long 1000 mg	box x 50 mini-sachets containing prolonged-release mini-tablets	1000 mg	sodium valproate	Desitin Arzneimittel GmbH, Germany	18001949	voluntary recall at distributor level, following an out of specification result for parameter "Active substance dosage"	Voluntary recall and destruction	27.08.2020
5	Binocrit 30000 IU/0.75 ml	solution for injection in pre-filled syringe	30000 IU/0.75 ml	epoetin alfa	Hexal Biotech Forschungs GmbH-Germany/Sandoz GmbH-Austria	1910020044	voluntary recall from the market, at pharmacy level, following out of specification results approved for parameter	Voluntary recall and destruction	30.09.2020

							"Met(54)Ox" (following extension of investigations performed by manufacturer)		
6	Binocrit 40000 IU/1 ml	solution for injection in pre-filled syringe	40000 IU/1 ml	epoetin alfa	Hexal Biotech Forschungs GmbH-Germany/Sandoz GmbH-Austria	1909040004, 1912130040, 2002030075	voluntary recall from the market, at pharmacy level, following out of specification results approved for parameter "Met(54)Ox" (following extension of investigations performed by manufacturer)	Voluntary recall and destruction	30.09.2020
7	Analgex 400 mg/325 mg	film-coated tablets	400 mg/ 325 mg	combinations (ibuprofen+ paracetamol)	Laropharm SRL	M02241	voluntary recall from the market, at pharmacy level, following identification of an imprinting error on the secondary packaging	Voluntary recall and destruction	30.09.2020

Applications for marketing authorisation/marketing authorisation renewal received during the 2nd quarter of 2020

13 applications for marketing authorisation/marketing authorisation renewal were received during the 2nd quarter of 2020 for medicinal products belonging to the following therapeutic groups:

INN	Trade name	Pharmaceutical form	Strength	MAH	Holding country	ATC code	Status
PARACETAMOL + PSEUDOEPHEDRINE HYDROCHLORIDE + DEXTROMETHORPHAN HYDROBROMIDE	Gripex Max	film-coated tablets	500mg/30mg/15mg	Nusafe Sp. z o.o. Poleczki 35 street 02-822 Warsaw, Poland	POLAND	N02BE51	A
GEFITINIB	GEFITINIB POLISANO 250 mg film-coated tablets	film-coated tablets	250 mg	POLISANO PHARMACEUTICALS S.A. 156 Şoseaua Alba Iulia, Sibiu, Romania	ROMANIA	L01XE02	A
PARACETAMOL + ASCORBIC ACID + PHENYLEPHRINE HYDROCHLORIDE	GRIPEX HOT MAX Gripex powder for oral suspension	powder for oral suspension	1000mg/100mg/12,2mg	NUSAFE Sp. z o.o. Poleczki 35 street 02-822, Warsaw, Poland	POLAND	N02BE51	A

PARACETAMOL + PSEUDOEPHEDRINE HYDROCHLORIDE + ASCORBIC ACID	GRIPEX HOT SINUS powder for oral suspension	powder for oral suspension	60mg/20mg/4mg	Nusafe Sp. z o.o. Address Poleczki 35 street 02-822, Warsaw, POLAND	POLAND	N02BE51	A
BUTYLSCOPOLAMINE BROMIDE	SCOBUSAL 10 mg tablets	tablets	10 mg	S.C.Slavia Pharm S.R.L. 44C Theodor Pallady, sector 3, Bucharest Romania	ROMANIA	A03BB01	R
AMBAZONE MONOHYDRATE	FARINGOSEPT Miere și Lămâie 10 mg orodispersible tablets	orodispersible tablets	10 mg	Terapia S.A. 124 Strada Fabricii, Cuj-Napoca, Romania	ROMANIA	R01AA01	R
AMBAZONE MONOHYDRATE	FARINGOSEPT Fructe de pădure 10 mg orodispersible tablets	orodispersible tablets	10 mg	Terapia S.A. 124 Strada Fabricii, Cuj-Napoca, Romania	ROMANIA	R01AA01	R
AMBAZONE MONOHYDRATE	FARINGOSEPT Vanilie 10 mg orodispersible tablets	orodispersible tablets	10 mg	Terapia S.A. 124 Strada Fabricii, Cuj-Napoca, Romania	ROMANIA	R01AA01	R
AMBAZONE MONOHYDRATE	FARINGOSEPT CAFEA 10 mg orodispersible tablets	orodispersible tablets	10 mg	Terapia S.A. 124 Strada Fabricii, Cuj-Napoca, Romania	ROMANIA	R01AA01	R

TRIPTORELIN PAMOATE	DIPHERELINE 22.5 mg prolonged-release powder and solvent for suspension for injection	prolonged-release powder and solvent for suspension for injection	22.5 mg	Ipsen Pharma 65 Quai Georges Gorse, 92100 Boulogne Billancourt, France	FRANCE	L02AE04	R
CANDESARTAN CILEXETIL	Candesartan Atb 8 mg tablets	tablets	8 mg	S.C.ANTIBIOTICE S.A 1 Valea Lupului, Iaşi, Iaşi county, cod 707410 Iaşi, Romania "	ROMANIA	C09CA06	R
CANDESARTAN CILEXETIL	Candesartan Atb 16 mg tablets	tablets	16 mg	S.C.ANTIBIOTICE S.A 1 Valea Lupului, Iaşi, Iaşi county, cod 707410 Iaşi, Romania "	ROMANIA	C09CA06	R
PARACETAMOL + ASCORBIC ACID + PHENYLEPHRINE HYDROCHLORIDE	COLDREX MaxGrip Fructe de pădure & Mentol powder for oral suspension	powder for oral suspension	1000mg/70mg/10mg	HIPOCRATE 2000 S.R.L. 6A Prahova, Sector 1, Bucharest, Romania	ROMANIA	N02BE51	R

Medicinal products authorised for marketing during the 2nd quarter of 2020

INN	Trade name	Pharmaceutical form	Strength	MAH	Holding country	MA no.		
ACICLOVIRUM	ACICLOVIR ACCORD	concentrate for solution for infusion	25mg/ml	ACCORD HEALTHCARE LTD.	UK	13194	2020	01
ACICLOVIRUM	HERPEXID	cream	50mg/g	SLAVIA PHARM S.R.L.	ROMANIA	13295	2020	01
ACIDUM FOLICUM	ACID FOLIC BIOFARM	tablets	5mg	BIOFARM S.A.	ROMANIA	13262	2020	01
AMISULPRIDUM	AKTYPROL	tablets	200mg	MEDOCHEMIE LTD	CYPRUS	13270	2020	01
AMISULPRIDUM	AKTYPROL	tablets	400mg	MEDOCHEMIE LTD	CYPRUS	13271	2020	01
ARIPIPRAZOLUM	ZYKALOR	tablets	5mg	MEDOCHEMIE LTD	CYPRUS	13105	2020	01
ARIPIPRAZOLUM	ZYKALOR	tablets	10mg	MEDOCHEMIE LTD	CYPRUS	13106	2020	01
ARIPIPRAZOLUM	ZYKALOR	tablets	15mg	MEDOCHEMIE LTD	CYPRUS	13107	2020	01
ARIPIPRAZOLUM	ZYKALOR	tablets	20mg	MEDOCHEMIE LTD	CYPRUS	13108	2020	01
ARIPIPRAZOLUM	ZYKALOR	tablets	30mg	MEDOCHEMIE LTD	CYPRUS	13109	2020	01
ARIPIPRAZOLUM	ARIPIPRAZOL ACCORD HEALTHCARE	tablets	15mg	ACCORD HEALTHCARE B.V	HOLLAND	13229	2020	01
ARIPIPRAZOLUM	ARIPIPRAZOL ACCORD HEALTHCARE	tablets	10mg	ACCORD HEALTHCARE B.V	HOLLAND	13228	2020	01
AZACITIDINEUM	AZACITIDINA ZENTIVA	powder for solution for injection	25mg/ml	ZENTIVA k.s.	THE CZECH REPUBLIC	13091	2020	01

AZACITINEUM	LAZIROS	powder for oral suspension	25mg/ml	STADA ARZNEIMITTEL AG	GERMANY	13217	2020	01
BECLOMETASONUM DIPROPIONATE+ FORMOTEROLUM FUMARATE	FOSTER NEXTHALER	inhalation powder	200mcg/ 12mcg	CHIESI FARMACEUTICI SPA	ITALY	13226	2020	01
BENZIDAMINUM HYDROCHLORIDE/ CETYLPYRIDIUM	FARINGOSEPT	oromucosal spray, solution	1.5mg/ ml	TERAPIA S.A	ROMANIA	13110	2020	01
BENZIDAMINUM HYDROCHLORIDE/ CETYLPYRIDIUM	FARINGOSEPT	oromucosal spray, solution	3mg/ml	TERAPIA S.A	ROMANIA	13111	2020	01
BETAHISTIDINUM DICLORHIDRATUM	BETAHISTINA LPH	tablets	8mg	LABORMED PHARMA S.A.	ROMANIA	13143	2020	01
BETAHISTIDINUM DICLORHIDRATUM	BETAHISTINA LPH	tablets	16mg	LABORMED PHARMA S.A.	ROMANIA	13144	2020	01
BETAHISTINUM	BETAHISTINA LPH	tablets	24mg	LABORMED PHARMA S.A.	ROMANIA	13145	2020	01
BORTEZOMIBUM	BORTEZOMIB ZENTIVA	powder for solution for injection	3.5mg	ZENTIVA k.s.	THE CZECH REPUBLIC	13085	2020	01
BORTEZOMIBUM	ZEGOMIB	powder for solution for injection	1mg	EGIS PHARMACEUTICALS PLC	HUNGARY	13088	2020	01
BORTEZOMIBUM	ZEGOMIB	powder for solution for injection	3.5mg	EGIS PHARMACEUTICALS PLC	HUNGARY	13089	2020	01

CAPTOPRILUM	CAPTOPRIL LAROPHARM	tablets	25 mg	LAROPHARM S.R.L.	ROMANIA	13173	2020	01
CEFACLORUM	CEFACLOR ARENA	capsules	250 mg	ARENA GROUP S.A.	ROMANIA	13257	2020	01
CEFTAZIDIMUM	CEFTAZIDIMA MIP	powder for solution for injection/infusion	1g	MIP PHARMA GmbH	GERMANY	13182	2020	01
CEFTAZIDIMUM	CEFTAZIDIMA MIP	powder for solution for injection/infusion	2g	MIP PHARMA GmbH	GERMANY	13183	2020	01
CETIRIZINUM DIHYDROCHLORIDE	CELERG	film-coated tablets	10 mg	AC HELCOR SRL	ROMANIA	13292	2020	01
CILOSTAZOLUM	DILVAS	tablets	100mg	LABORATORY REIG JOFRE S.A.	ROMANIA	13086	2020	01
CINACALCETUM	CINACALCET HEATON	film-coated tablets	30mg	HEATON K.S	THE CZECH REPUBLIC	13248	2020	01
BETAXOLOL HYDROCHLORIDE	BETAC	film-coated tablets	20 mg	MEDOCHEMIE LTD	CYPRUS	13253	2020	01
PHENYLEPHRINE HYDROCHLORIDE	SER EFEDRINAT	nasal drops, solution	5 mg/ml	TIS FARMACEUTIC S.A.	ROMANIA	13259	2020	01
PHENYLEPHRINE HYDROCHLORIDE	SER EFEDRINAT	nasal drops, solution	10 mg/ml	TIS FARMACEUTIC S.A.	ROMANIA	13260	2020	01
CLORHIDRATUM AMITRIPTILINUM	AMITRIPTILINA ARENA	film-coated tablets	25mg	ARENA GROUP S.A.	ROMANIA	13252	2020	01
MINOCYCLINE HYDROCHLORIDE	MINOZ EP	prolonged-release capsules	100 mg	TERAPIA S.A	ROMANIA	13164	2020	01
CLOTRIMAZOLUM	CLOTRIMAZOL ROMPHARM	cutaneous spray, solution	10mg/ml	ROMPHARM COMPANY S.R.L.	ROMANIA	13263	2020	01

COMBINATIONS	TRAVOCORT	cream		LEO PHARMA A/S	DENMARK	13121	2020	01
COMBINATIONS	SANADOR SINUS	film-coated tablets	500mg/ 30mg	LAROPHARM S.R.L.	ROMANIA	13141	2020	01
COMBINATIONS	ZYMOGEN FORTE	gastroresistant film-coated tablets		FELSIN FARM. S.R.L.	ROMANIA	13149	2020	01
COMBINATIONS	NEVRALGIO	tablets	250 mg/ 150 mg/ 20 mg	SINTOFARM S.A.	ROMANIA	13152	2020	01
COMBINATIONS	FARINGOSEPT COMBO MENTA	pills		TERAPIA S.A	ROMANIA	13177	2020	01
COMBINATIONS	FARINGOSEPT COMBO MIERE SI LAMAIE	pills		TERAPIA S.A	ROMANIA	13178	2020	01
COMBINATIONS	FARINGOSEPT RAPID MENTA	pills	2 mg/ 0.6 mg/ 1.2 mg	TERAPIA S.A	ROMANIA	13220	2020	01
COMBINATIONS	FARINGOSEPT RAPID MIERE SI LAMAIE	pills	2 mg/ 0.6 mg/ 1.2 mg	TERAPIA S.A	ROMANIA	13222	2020	01
COMBINATIONS	FARINGOSEPT RAPID PORTOCALE	pills	2 mg/ 0.6 mg/ 1.2 mg	TERAPIA S.A	ROMANIA	13221	2020	01
COMBINATIONS	SOLUTIE RINGER FRESENIUS	solution for infusion		FRESENIUS KABI DEUTSCHLAND GMBH	GERMANY	13305	2020	01
COMBINATIONS	SOLUTIE RINGER LACTAT FRESENIUS	solution for infusion		FRESENIUS KABI DEUTSCHLAND GMBH	GERMANY	13306	2020	01

DAPOXETINUM HYDROCHLORIDE	PLOTIS	film-coated tablets	30mg	MEDOCHEMIE LTD	CYPRUS	13207	2020	01
DAPOXETINUM HYDROCHLORIDE	PLOTIS	film-coated tablets	60mg	MEDOCHEMIE LTD	CYPRUS	13208	2020	01
DEFERASIROXUM	REDITENS	film-coated tablets	90mg	DR. REDDY'S LABORATORIES ROMANIA SRL	ROMANIA	13272	2020	01
DEFERASIROXUM	REDITENS	film-coated tablets	180mg	DR. REDDY'S LABORATORIES ROMANIA SRL	ROMANIA	13273	2020	01
DEFERASIROXUM	REDITENS	film-coated tablets	360mg	DR. REDDY'S LABORATORIES ROMANIA SRL	GERMANY	13274	2020	01
DEFERASIROXUM	DEFERASIROX ZENTIVA	film-coated tablets	90mg	ZENTIVA k.s.	THE CZECH REPUBLIC	13285	2020	01
DEFERASIROXUM	DEFERASIROX ZENTIVA	film-coated tablets	180mg	ZENTIVA k.s.	THE CZECH REPUBLIC	13286	2020	01
DEFERASIROXUM	DEFERASIROX ZENTIVA	film-coated tablets	360mg	ZENTIVA k.s.	THE CZECH REPUBLIC	13287	2020	01
DICLORHIDRATUM DE CETIRIZINUM	CETIRIZINA HELCOR	film-coated tablets	10 mg	AC HELCOR PHARMA SRL	ROMANIA	13268	2020	01
DIFENHIDRAMINUM CLORHIDRAT	RIVAL	gel	20mg/g	FITERMAN PHARMA SRL	ROMANIA	13172	2020	01
DILTIAZEMUM HYDROCHLORIDE	DILTIAZEM LPH	tablets	60mg	LABORMED PHARMA S.A.	ROMANIA	13154	2020	01
DIOSMINUM	DETRALEX	film-coated tablets	1000mg	LES LABORATORIES SERVIER	FRANCE	13151	2020	01
DOMPERIDONUM	DOMOTIL	orodispersible tablets	10mg	LABORMED PHARMA S.A.	ROMANIA	13099	2020	01

DONEPEZILUM HYDROCHLORIDE	DAVIA	film-coated tablets	5 mg	TERAPIA S.A.	ROMANIA	13147	2020	01
DONEPEZILUM HYDROCHLORIDE	DAVIA	film-coated tablets	10 mg	TERAPIA S.A.	ROMANIA	13148	2020	01
DONEPEZILUM HYDROCHLORIDE	DARIZOL	orodispersible tablets	5mg	NEOLA PHARMA SRL	ROMANIA	13155	2020	01
DONEPEZILUM HYDROCHLORIDE	DARIZOL	orodispersible tablets	10mg	NEOLA PHARMA SRL	ROMANIA	13156	2020	01
DULOXETINUM HYDROCHLORIDUM	DULASOLAN	capsules	30mg	G.L PHARMA GMBH	AUSTRIA	13094	2020	01
DULOXETINUM HYDROCHLORIDUM	DULASOLAN	capsules	60mg	G.L PHARMA GMBH	AUSTRIA	13095	2020	01
EMTRICITABINUM/ TENOFOVIRUM DISOPEOXILUM FUMARATE	EMTRICITABINA/ TENOFOVIR DISOPROXIL TILLOMED	film-coated tablets	200mg/ 245mg	TILLOMED PHARMA GMBH	GERMANY	13275	2020	01
ENOXAPARINUM SODIUM	HEPAXANE	solution for injection (pre-filled syringe)	10000 IU/ 1 ml	ITALFARMACO S.P.A.	ITALY	13234	2020	01
ENOXAPARINUM SODIUM	HEPAXANE	solution for injection (pre-filled syringe)	15000 IU/ 1 ml	ITALFARMACO S.P.A.	ITALY	13236	2020	01
ENOXAPARINUM SODIUM	HEPAXANE	solution for injection (pre-filled syringe)	2000 IU/ 0.2 ml	ITALFARMACO S.P.A.	ITALY	13230	2020	01
ENOXAPARINUM SODIUM	HEPAXANE	solution for injection (pre-filled syringe)	4000 IU/ 0.4 ml	ITALFARMACO S.P.A.	ITALY	13231	2020	01

ENOXAPARINUM SODIUM	HEPAXANE	solution for injection (pre-filled syringe)	6000 IU/ 0.6 ml	ITALFARMACO S.P.A.	ITALY	13232	2020	01
ENOXAPARINUM SODIUM	HEPAXANE	solution for injection (pre-filled syringe)	8000 IU/ 0.8 ml	ITALFARMACO S.P.A.	ITALY	13233	2020	01
ENOXAPARINUM SODIUM	HEPAXANE	solution for injection (pre-filled syringe)	12000 IU/ 0.8 ml	ITALFARMACO S.P.A.	ITALY	13235	2020	01
ERLOTINIBUM	ERLOTINIB KRKA	film-coated tablets	25mg	KRKA D.D. NOVO MESTO	SLOVENIA	13100	2020	01
ERLOTINIBUM	ERLOTINIB KRKA	film-coated tablets	100mg	KRKA D.D. NOVO MESTO	SLOVENIA	13101	2020	01
ERLOTINIBUM	ERLOTINIB KRKA	film-coated tablets	150mg	KRKA D.D. NOVO MESTO	SLOVENIA	13102	2020	01
ESTRADIOLUM HEMYHIDRATE	ESTRADIOL BESINS	transdermal gel	0.75 mg/ dose	BESINS HEALTHCARE SA	BELGIUM	13093	2020	01
FLUCONAZOLUM	FLUCONAZOL MEDOCHEMIE	capsules	50 mg	MEDOCHEMIE ROMANIA S.R.L.	ROMANIA	13118	2020	01
FLUCONAZOLUM	FLUCONAZOL MEDOCHEMIE	capsules	150 mg	MEDOCHEMIE ROMANIA S.R.L.	ROMANIA	13119	2020	01
FLUCONAZOLUM	FLUVAZOL	capsules	150 mg	SLAVIA PHARMA S.R.L.	ROMANIA	13166	2020	01
FLURBIPROFENUM	MARTIFEN	orodispersible tablets	8.75mg	GEISER PHARMA	SPAIN	13096	2020	01
FLURBIPROFENUM	STREPSILS INTENSIV CIRESE SI MENTA	oromucosal spray, solution	8.75mg	RECKITT BENCKISER ROMANIA	ROMANIA	13092	2020	01

GANCICLOVIRUM	VIRGAN	eye gel	1.5mg/g	LABORATOIRES THEA	FRANCE	13277	2020	01
GINKGO BILOBA	TANAKAN	tablets	40 mg	IPSEN PHARMA GmbH	FRANCE	13168	2020	01
GLICLAZIDUM	DIAPHAN MR	Modified-release tablets	60mg	ANPHARM S.A.	POLAND	13307	2020	01
HOMEOPATE	NEUREXAN	tablets		BIOLOGISCHE HEILMITTEL HEEL GMBH	GERMANY	13097	2020	01
HOMEOPATE	STODALINE FARA ZAHAR	syrup		BOIRON	FRANCE	13150	2020	01
HUMAN PLASMA COAGULATION FACTORS	PRONATIV	powder and solvent for solution for infusion	25 IU/ ml	OCTAPHARMA SPRL	BELGIUM	13251	2020	01
IBUPROFENUM	IBUPROFEN B BRAUN	solution for injection	200 mg	B. BRAUN MEDICAL S.A.	GERMANY	13087	2020	01
IBUPROFENUM	IBUPROFEN DR MAX	capsules	400mg	DR MAX PHARMA SRO	THE CZECH REPUBLIC	13112	2020	01
IBUPROFENUM	RUPAN	tablets	200 mg	MEDOCHEMIE LTD	CYPRUS	13159	2020	01
IBUPROFENUM	ADVIL ULTRA FORTE	soft capsules	400 mg	PFIZER CORPORATION AUSTRIA	AUSTRIA	13258	2020	01
IBUPROFENUM	IBUPROFEN ARENA	capsules	200 mg	ARENA GROUP S.A.	ROMANIA	13280	2020	01
IBUPROFENUM	ADVIL	lozenges	200mg	GLAXOSMITHKLINE CONSUMER HEALTHCARE	ROMANIA	13301	2020	01
IBUPROFENUM/ CAFFEINE	IBALGIN DUO	film-coated tablets	400mg/ 100mg	SANOFI ROMANIA SRL	ROMANIA	13115	2020	01

IMIPENEM/ CILASTATIN	CILOPEN	powder for solution for infusion	500 mg/ 500 mg	TERAPIA S.A.	ROMANIA	13122	2020	01
INDAPAMIDUM	INDAPAMIDA ATB	prolonged-release tablets	1.5mg	ANTIBIOTICE S.A.	ROMANIA	13264	2020	01
INDOMETACINUM	INDOMETACIN FITERMAN	cream	40 mg/g	FITERMAN PHARMA SRL	ROMANIA	13293	2020	01
IRBESARTANUM/ AMLOPIDINUM BESILATE	APREXEVO	film-coated tablets	150mg/ 5mg	SANOFI ROMANIA SRL	ROMANIA	13281	2020	01
IRBESARTANUM/ AMLOPIDINUM BESILATE	APREXEVO	film-coated tablets	150mg/ 10mg	SANOFI ROMANIA SRL	ROMANIA	13282	2020	01
IRBESARTANUM/ AMLOPIDINUM BESILATE	APREXEVO	film-coated tablets	300mg/ 5mg	SANOFI ROMANIA SRL	ROMANIA	13283	2020	01
IRBESARTANUM/ AMLOPIDINUM BESILATE	APREXEVO	film-coated tablets	300mg/ 10mg	SANOFI ROMANIA SRL	ROMANIA	13284	2020	01
ISOFLURANUM	AERRANE	liquid for inhalation vapours		BAXTER SA	BELGIUM	13267	2020	01
IZOCONAZOLUM NITRATE	TRAVOGEN	cream	10mg/1g	LEO PHARMA A/S	DENMARK	13120	2020	01
KANAMYCINUM SULPHATE	KANAMICINA PAN PHARMA	powder for concentrate for solution for infusion/injection	1g	PANPHARMA	FRANCE	13176	2020	01
KETOCONAZOLUM	KETOCONAZOL FITERMAN	cream	20 mg/g	FITERMAN PHARMA SRL	ROMANIA	13261	2020	01

LATANOPROSTUM	VIZILATAN	eye drops, solution	50mcg/ ml	BAUSCH HEALTH IRELAND LIMITED	IRELAND	13289	2020	01
LATANOPROSTUM/ TIMOLOLUM MALEATE	VIZILATAN DUO	eye drops, solution	0.05 mg/ml +5 mg/ml	BAUSCH HEALTH LIMITED	IRELAND	13216	2020	01
LEVOTHYROXINUM SODIUM	LEVOTIROXINA ACCORD	tablets	12.5mcg	ACCORD HEALTHCARE POLSKA Sp z.o.o.	POLAND	13125	2020	01
LEVOTHYROXINUM SODIUM	LEVOTIROXINA ACCORD	tablets	25 mg	ACCORD HEALTHCARE POLKA Sp.z o.o.	POLAND	13126	2020	01
LEVOTHYROXINUM SODIUM	LEVOTIROXINA ACCORD	tablets	50mcg	ACCORD HEALTHCARE LIMITED	POLAND	13127	2020	01
LEVOTHYROXINUM SODIUM	LEVOTIROXINA ACCORD	tablets	75mcg	ACCORD HEALTHCARE LIMITED	POLAND	13128	2020	01
LEVOTHYROXINUM SODIUM	LEVOTIROXINA ACCORD	tablets	88mcg	ACCORD HEALTHCARE LIMITED	POLAND	13129	2020	01
LEVOTHYROXINUM SODIUM	LEVOTIROXINA ACCORD	tablets	100mcg	ACCORD HEALTHCARE LIMITED	POLAND	13130	2020	01
LEVOTHYROXINUM SODIUM	LEVOTIROXINA ACCORD	tablets	112mcg	ACCORD HEALTHCARE LIMITED	POLAND	13131	2020	01

LEVOTHYROXINUM SODIUM	LEVOTIROXINA ACCORD	tablets	125mcg	ACCORD HEALTHCARE LIMITED	POLAND	13132	2020	01
LEVOTHYROXINUM SODIUM	LEVOTIROXINA ACCORD	tablets	137mcg	ACCORD HEALTHCARE LIMITED	POLAND	13133	2020	01
LEVOTHYROXINUM SODIUM	LEVOTIROXINA ACCORD	tablets	150mcg	ACCORD HEALTHCARE LIMITED	POLAND	13134	2020	01
LEVOTHYROXINUM SODIUM	LEVOTIROXINA ACCORD	tablets	175mcg	ACCORD HEALTHCARE LIMITED	POLAND	13135	2020	01
LEVOTHYROXINUM SODIUM	LEVOTIROXINA ACCORD	tablets	200mcg	ACCORD HEALTHCARE LIMITED	POLAND	13136	2020	01
LEVOTHYROXINUM SODIUM	ACCU-THYROX	oral solution	25mcg	GALENICA S.A.	GREECE	13179	2020	01
LEVOTHYROXINUM SODIUM	ACCU-THYROX	oral solution	50mcg	GALENICA S.A.	GREECE	13180	2020	01
LEVOTHYROXINUM SODIUM	ACCU-THYROX	oral solution	100mcg	GALENICA S.A.	GREECE	13181	2020	01
LINEZOLIDUM	LINEZOLID KRKA	film-coated tablets	600mg	KRKA D.D. NOVO MESTO	SLOVENIA	13184	2020	01
LOPERAMIDUM	ENTERIUM	capsules	2mg	SC SANIENCE SRL	ROMANIA	13265	2020	01
LORATADINUM	LOPYOL	capsules	2 mg	SLAVIA PHARM	ROMANIA	13296	2020	01
MELPHALANUM HYDROCHLORIDUM	MELPHALAN KOANAA	powder and solvent for solution for infusion	50mg	AMRING FARMA SRL	ROMANIA	13114	2020	01

METOPROLOLUM TARTRATE/ IVABRADINUM	IMPLICOR	film-coated tablets	25mg/ 5mg	LES LAB. SERVIER	FRANCE	13137	2020	01
METOPROLOLUM TARTRATE/ IVABRADINUM	IMPLICOR	film-coated tablets	50mg/ 5mg	LES LAB. SERVIER	FRANCE	13138	2020	01
METOPROLOLUM TARTRATE/ IVABRADINUM	IMPLICOR	film-coated tablets	25mg/ 7.5mg	LES LAB. SERVIER	FRANCE	13139	2020	01
METOPROLOLUM TARTRATE/ IVABRADINUM	IMPLICOR	film-coated tablets	50mg/ 7.5mg	LES LAB. SERVIER	FRANCE	13140	2020	01
MOXIFLOXACINUM HYDROCHLORIDE	MOXIFLOXACINA ACCORD	film-coated tablets	400mg	ACCORD HEALTHCARE LIMITED	POLAND	13090	2020	01
NAPROXENUM	REUXEN 200 mg	tablets	200mg	AC HELCOR SRL	ROMANIA	13161	2020	01
NAPROXENUM	REUXEN 250 mg	tablets	250 mg	AC HELCOR SRL	ROMANIA	13162	2020	01
NAPROXENUM	REUXEN 500 mg	tablets	500 mg	AC HELCOR SRL	ROMANIA	13163	2020	01
NAPROXENUM SODIUM	NALGESIN	film-coated tablets	220mg	KRKA D.D. NOVO MESTO	SLOVENIA	13113	2020	01
NAPROXENUM SODIUM	NALDOREX	film-coated tablets	275mg	KRKA D.D. NOVO MESTO	SLOVENIA	13198	2020	01
NAPROXENUM SODIUM	NALDOREX	film-coated tablets	500mg	KRKA D.D. NOVO MESTO	SLOVENIA	13199	2020	01
NICOTINUM	NICORETTE BERRYMINT	oromucosal spray, solution	1mg/ spray	MCNEIL AB	SWEDEN	13175	2020	01

NOFLOXACINUM	NORFLOXACINA LPH 400 mg	film-coated tablets	400 mg	LABORMED PHARMA S.A.	ROMANIA	13158	2020	01
NOREPINEPHRINUM	NORADRENALINA KALCEKS	concentrate for solution for injection	1 mg/ml	AS KALCEKS	LATVIA	13246	2020	01
OLMESARTANUM/ AMLOPIDINUM/ HIDROCLOROTIAZIDUM	OLSITRI	film-coated tablets	20mg/ 5mg/ 12.5mg	KRKA D.D. NOVO MESTO	SLOVENIA	13210	2020	01
OLMESARTANUM/ AMLOPIDINUM/ HIDROCLOROTIAZIDUM	OLSITRI	film-coated tablets	40mg/ 5mg/ 12.5mg	KRKA D.D. NOVO MESTO	SLOVENIA	13211	2020	01
OLMESARTANUM/ AMLOPIDINUM/ HIDROCLOROTIAZIDUM	OLSITRI	film-coated tablets	40mg/ 5mg/ 25mg	KRKA D.D. NOVO MESTO	SLOVENIA	13212	2020	01
OLMESARTANUM/ AMLOPIDINUM/ HIDROCLOROTIAZIDUM	OLSITRI	film-coated tablets	40mg/ 10mg/ 12.5mg	KRKA D.D. NOVO MESTO	SLOVENIA	13213	2020	01
OLMESARTANUM/ AMLOPIDINUM/ HIDROCLOROTIAZIDUM	OLSITRI	film-coated tablets	40mg/ 10mg/ 25mg	KRKA D.D. NOVO MESTO	SLOVENIA	13214	2020	01
OMEPRAZOLUM	OMEPRAZOL DR. REDDY'S	gastroresistant capsules	20mg	DR. REDDY'S LABORATORIES	ROMANIA	13123	2020	01
OMEPRAZOLUM	OMEPRAZOL ALVOGEN	gastroresistant capsules	20mg	ALVOGEN PHARMA TRADING	BULGARIA	13247	2020	01
ONDASETRONUM HYDROCHLORIDE	ONDASETRON ACCORD	solution for injection (pre-filled syringe)	4mg	ACCORD HEALTHCARE BV	HOLLAND	13103	2020	01

ONDASETRONUM HYDROCHLORIDE	ONDASETRON ACCORD	solution for injection (pre-filled syringe)	8mg	ACCORD HEALTHCARE BV	HOLLAND	13104	2020	01
OSELTAMIVIRUM	OSELTAMIVIR MSN	capsules	30mg	VIVANTA GENERICS sro	THE CZECH REPUBLIC	13201	2020	01
OSELTAMIVIRUM	OSELTAMIVIR MSN	capsules	45mg	VIVANTA GENERICS sro	THE CZECH REPUBLIC	13202	2020	01
OSELTAMIVIRUM	OSELTAMIVIR MSN	capsules	75mg	VIVANTA GENERICS sro	THE CZECH REPUBLIC	13203	2020	01
PARACETAMOLUM	PARACETAMOL POLISANO	tablets	500mg	POLISANO PHARMACEUTICALS	ROMANIA	13098	2020	01
PARACETAMOLUM	PARACETAMOL TERAPIA	tablets	500mg	TERAPIA SA	ROMANIA	13157	2020	01
PARACETAMOLUM	PARACETAMOL ATB	tablets	500mg	ANTIBIOTICE S.A.	ROMANIA	13174	2020	01
PARACETAMOLUM/ CAFEINUM	PANACIT EXTRA	tablets	500mg/ 65mg	DR MAX PHARMA	THE CZECH REPUBLIC	13204	2020	01
PARACETAMOLUM/ IBUPROFENUM	COMBOGESIC	film-coated tablets	500mg/ 150mg	SWIXX BIOPHARMA KFT	HUNGARY	13117	2020	01
PARACETAMOLUM/ IBUPROFENUM	PARACETAMOL IBUPROFEN VALE	solution for infusion	3mg/ 100ml	VALE PHARMACEUTICALS LTD.	IRELAND	13300	2020	01
PENICILINUM	OSPEN 400.000UI	oral suspension	400.000IU/ 5ml	SANDOZ GmbH	AUSTRIA	13256	2020	01
PENTOXIFYLLINUM	VASONIT RETARD	prolonged-release tablets	600 mg	LANNACHER HEILMITTEL Ges.m.b.H	AUSTRIA	13167	2020	01
PIROXICAMUM	PIROXICAM LAROPHARM 20 mg	tablets	20 mg	LAROPHARM S.R.L.	ROMANIA	13266	2020	01

PRANOPROFENUM	PRANOFLOG	eye drops, solution	1 mg/ml	S.I.F.I S.p.A	ITALY	13153	2020	01
BIOLOGICAL PRODUCTS	ALUTARD SQ VENIN DE VIESPE	suspension for injection	100.000 SQ-U/mL	ALK - ABELLO A/S	SPAIN	13239	2020	01
BIOLOGICAL PRODUCTS	ALUTARD SQ VENIN DE VIESPE	suspension for injection	100.000 SQ-U/mL	ALK - ABELLO A/S	SPAIN	13240	2020	01
BIOLOGICAL PRODUCTS	ALUTARD SQ VENIN DE ALBINA	suspension for injection	100.000 SQ.U/ml	ALK - ABELLO A/S	DENMARK	13237	2020	01
BIOLOGICAL PRODUCTS	ALUTARD SQ VENIN DE ALBINA	suspension for injection	100.000 SQ.U/ml	ALK - ABELLO A/S	DENMARK	13238	2020	01
BIOLOGICAL PRODUCTS	EFLUELDA	suspension for injection	60mcg	SANOFI PASTEUR	FRANCE	13227	2020	01
BIOLOGICAL PRODUCTS	GELOPLASMA	solution for infusion	3g/100ml	FRESENIUS KABI ROMANIA S.R.L.	ROMANIA	13288	2020	01
BIOLOGICAL PRODUCTS	BERINERT	powder and solvent for solution for injection	1500 IU	CSL BEHRING GmbH	GERMANY	13297	2020	01
BIOLOGICAL PRODUCTS	BERINERT	powder and solvent for solution for injection	2000 IU	CSL BEHRING GmbH	GERMANY	13298	2020	01
BIOLOGICAL PRODUCTS	BERINERT	powder and solvent for solution for injection	3000 IU	CSL BEHRING GmbH	GERMANY	13299	2020	01
PROGESTERONUM	AREFAM	capsules	200 mg	PHARMASWISS CESKA REPUBLIKA s.r.o.	THE CZECH REPUBLIC	13165	2020	01

PROGESTERONUM	CRINONE	gel vaginal	80mg/ml	MERCK ROMANIA SRL	ROMANIA	13223	2020	01
QUETIAPINUM FUMARATE	QUETIAPINA ACCORD	film-coated tablets	25mg	ACCORD HEALTHCARE LIMITED	UK	13241	2020	01
QUETIAPINUM FUMARATE	QUETIAPINA ACCORD	film-coated tablets	100mg	ACCORD HEALTHCARE LIMITED	UK	13242	2020	01
QUETIAPINUM FUMARATE	QUETIAPINA ACCORD	film-coated tablets	150mg	ACCORD HEALTHCARE LIMITED	UK	13243	2020	01
QUETIAPINUM FUMARATE	QUETIAPINA ACCORD	film-coated tablets	200mg	ACCORD HEALTHCARE LIMITED	UK	13244	2020	01
QUETIAPINUM FUMARATE	QUETIAPINA ACCORD	film-coated tablets	300mg	ACCORD HEALTHCARE LIMITED	UK	13245	2020	01
RASAGILINUM	SAGILIA	tablets	1mg	MEDOCHEMIE LTD	CYPRUS	13219	2020	01
RASAGILINUM TARTRATE	RASAGILINA AUROBINDO	tablets	1mg	AUROBINDO PHARMA ROMANIA SRL	ROMANIA	13250	2020	01
RIVAROXABANUM	XANIRVA	capsules	2.5mg	ZENTIVA k.s.	THE CZECH REPUBLIC	13189	2020	01
RIVAROXABANUM	XANIRVA	capsules	10mg	ZENTIVA k.s.	THE CZECH REPUBLIC	13190	2020	01
RIVAROXABANUM	XANIRVA	capsules	15mg	ZENTIVA k.s.	THE CZECH REPUBLIC	13191	2020	01
RIVAROXABANUM	XANIRVA	capsules	20mg	ZENTIVA k.s.	THE CZECH REPUBLIC	13192	2020	01

RIVAROXABANUM	XERDOXO	film-coated tablets	2.5 mg	KRKA D.D. NOVO MESTO	SLOVENIA	13185	2020	01
RIVAROXABANUM	XERDOXO	film-coated tablets	10 mg	KRKA D.D. NOVO MESTO	SLOVENIA	13186	2020	01
RIVAROXABANUM	XERDOXO	film-coated tablets	15 mg	KRKA D.D. NOVO MESTO	SLOVENIA	13187	2020	01
RIVAROXABANUM	XERDOXO	film-coated tablets	20 mg	KRKA D.D. NOVO MESTO	SLOVENIA	13188	2020	01
ROPINIROLUM HYDROCHLORIDE	REQUIP MODUTAB	prolonged-release tablets	2 mg	GLAXOSMITHKLINE IRELAND LIMITED	IRELAND	13169	2020	01
ROPINIROLUM HYDROCHLORIDE	REQUIP MODUTAB	prolonged-release tablets	4 mg	GLAXOSMITHKLINE IRELAND LIMITED	IRELAND	13170	2020	01
ROPINIROLUM HYDROCHLORIDE	REQUIP MODUTAB	prolonged-release tablets	8 mg	GLAXOSMITHKLINE IRELAND LIMITED	IRELAND	13171	2020	01
SACCHAROMYCES BOULARDII	ENTEROL	capsules	250 mg	BIOCODEX	FRANCE	13160	2020	01
SALBUTAMOLUM	SALBUTAMOL MCC 4 mg	tablets	4 mg	MAGISTRA C&C SRL	ROMANIA	13254	2020	01
SALMETEROLUM XINOFOATE + FLUTICAZONUM PROPIONATE	SERROFLO	pressurised suspension for inhalation	25mcg/ 125mcg	AMRING FARMA SRL	ROMANIA	13290	2020	01
SALMETEROLUM XINOFOATE + FLUTICAZONUM PROPIONATE	SERROFLO	pressurised suspension for inhalation	25mcg/ 250mcg	AMRING FARMA SRL	ROMANIA	13291	2020	01
SIMVASTATINUM	SIMVASTATIN TERAPIA	film-coated tablets	10mg	TERAPIA S.A	ROMANIA	13195	2020	01

SIMVASTATINUM	SIMVASTATIN TERAPIA	film-coated tablets	20mg	TERAPIA S.A	ROMANIA	13196	2020	01
SIMVASTATINUM	SIMVASTATIN TERAPIA	film-coated tablets	40mg	TERAPIA S.A	ROMANIA	13197	2020	01
SODIUM CHLORIDE;SODIUM CITRATE	REGIOCIT	solution for hemofiltration		GAMBRO LUNDIA AB	SWEDEN	13249	2020	01
SPIRONOLACTONUM	SPIRONOLACTONA ARENA	capsules	25 mg	ARENA GROUP S.A.	ROMANIA	13278	2020	01
SPIRONOLACTONUM	SPIRONOLACTONA ARENA	capsules	50 mg	ARENA GROUP S.A.	ROMANIA	13279	2020	01
BARIUM SULFATE	SULFAT DE BARIU MEDUMAN	powder for oral suspension	88.9g/ 100g	MEDUMAN S.A.	ROMANIA	13146	2020	01
HYDROXYCHLOROQUINE SULFATE	SULFAT DE HIDROCLOROCHINA ACCORD	film-coated tablets	200 mg	ACCORD HEALTHCARE LIMITED	POLAND	13200	2020	01
SUMATRIPTANUM	SUMATRIPTAN SUN	solution for injection	3mg/ 0.5ml	SUN PHARMACEUTICAL INDUSTRIES EUROPE B.V.	HOLLAND	13116	2020	01
TADALAFILUM	TADULAN	tablets	10 mg	STADA M&D SRL	ROMANIA	13205	2020	01
TADALAFILUM	TADULAN	tablets	20 mg	STADA M&D SRL	ROMANIA	13206	2020	01
PENTAERYTHRITOL TETRANITRATE	NITROPECTOR	tablets	20 mg	TERAPIA S.A.	ROMANIA	13142	2020	01
THALIDOMINUM	TALIDOMIDA ACCORD	capsules	50 mg	ACCORD HEALTHCARE LIMITED	IRELAND	13193	2020	01

TINIDAZOLUM	TIPROGYN	film-coated tablets	500mg	AC HELCOR SRL	ROMANIA	13255	2020	01
TIOTROPIUM BROMIDE	SRIVASSO	inhalation powder (capsule)	18mcg	BOEHRINGER INGELHEIM INT. GmbH	GERMANY	13225	2020	01
TIOTROPIUM BROMIDE/OLODATEROLUM HYDROCHLORIDE	SPIOLTO RESPIMAT	solution for inhalation	2.5mcg/ 2.5mcg	BOEHRINGER INGELHEIM INT. GmbH	GERMANY	13224	2020	01
VANCOMICINUM CLORHIDRATUM	VANCOMICINA MIP	powder for concentrate for solution for infusion	500mg	MIP PHARMA GmbH	GERMANY	13302	2020	01
VANCOMICINUM CLORHIDRATUM	VANCOMICINA MIP	powder for concentrate for solution for infusion	1000mg	MIP PHARMA GmbH	GERMANY	13303	2020	01
VIDAGLIPTINUM	GLUADDA	film-coated tablets	50mg	MERCK ROMANIA SRL	ROMANIA	13276	2020	01
VILDAGLIPTIMUN	AGARTHA	tablets	50mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	13215	2020	01
VILDAGLIPTIMUN	MELKART	tablets	50mg	G.L. PHARMA GMBH	AUSTRIA	13218	2020	01
VINORELBINUM TARTRATE	VINORELBINA TEVA	concentrate for solution for infusion	10mg/ml	TEVA PHARMA B.V.	HOLLAND	13124	2020	01
VORICONAZOLUM	VORICONAZOL FRESENIUS KABI	powder for solution for infusion	200mg	FRESENIUS KABI	BELGIUM	13269	2020	01

EMA centrally authorised medicinal products notified for marketing in Romania during the 2nd quarter of 2020

INN	Trade name	Pharmaceutical form	Strength	MAH	Holding country	MA number		
CINACALCETUM	CINACALCET ACCORDPHARMA 30 mg	film-coated tablets	30mg	ACCORD HEALTHCARE S.L.U.	SPAIN	1429	2020	02
COMBINATIONS (INDACATEROLUM+ MOMETASONUM)	ATECTURA BREEZHALER 125 micrograms/ 62.5 micrograms	powder for inhalation, capsules	125micrograms/ 62.5micrograms	NOVARTIS EUROPHARM LIMITED	IRELAND	1439	2020	02
COMBINATIONS (INDACATEROLUM+ MOMETASONUM)	ATECTURA BREEZHALER 125 micrograms/ 127.5 micrograms	powder for inhalation, capsules	125micrograms/ 127.5 micrograms	NOVARTIS EUROPHARM LIMITED	IRELAND	1439	2020	06
COMBINATIONS (INDACATEROLUM+ MOMETASONUM)	ATECTURA BREEZHALER 125 micrograms/ 260 micrograms	powder for inhalation, capsules	125micrograms/ 260micrograms	NOVARTIS EUROPHARM LIMITED	IRELAND	1439	2020	10
GLASDEGIB	DAURISMO 25 mg	film-coated tablets	25mg	PFIZER EUROPE MA EEG	BELGIUM	1923	2020	02
GLASDEGIB	DAURISMO 100 mg	film-coated tablets	100mg	PFIZER EUROPE MA EEIG	BELGIUM	1451	2020	02
INSULINUM LISPRO	LYUMJEV 100U/ml	solution for injection in pre-filled pen	100U/ml	ELI LILLY NEDERLAND B.V.	HOLLAND	1422	2020	08

INSULINUM LISPRO	LYUMJEV 200U/ml	solution for injection in pre-filled pen	200 U/ml	ELI LILLY NEDERLAND B.V.	HOLLAND	1422	2020	14
ISATUXIMABUM	SARCLISA 20 mg/ml	concentrate for oral solution	20mg/ml	SANOFI - AVENTIS GROUPE	FRANCE	1435	2020	03
LUSPATERCEPT	REBLOZYL 25 mg	powder for solution for injection	50mg/ml	CELGENE EUROPE B.V.	HOLLAND	1452	2020	01
LUSPATERCEPT	REBLOZYL 75 mg	powder for solution for injection	50mg/ml	CELGENE EUROPE B.V.	HOLLAND	1452	2020	02
ONASEMNOGEN ABEPARVOVEC	ZOLGENSMA	solution for infusion	2×1013 genomes vector/ml	AVEXIS EU LIMITED	IRELAND	1443	2020	37
OZANIMODUM	ZEPOSIA 0.23 mg/0.46 mg	capsules	0.23mg+ 0.46mg	BRISTOL-MYERS SQUIBB PHARMA EEIG	IRELAND	1442	2020	01
OZANIMODUM	ZEPOSIA 0.92 mg	capsules	0.92mg	BRISTOL-MYERS SQUIBB PHARMA EEIG	IRELAND	1442	2020	03
RITUXIMABUM	RUXIENCE 100mg	concentrate for solution for infusion	100mg	PFIZER EUROPE MA EEIG	BELGIUM	1431	2020	01
RITUXIMABUM	RUXIENCE 500mg	concentrate for solution for infusion	500mg	PFIZER EUROPE MA EEIG	BELGIUM	1431	2020	02
SEMAGLUTIDUM	RYBELSUS 3 mg	tablets	3 mg	NOVO NORDISK A/S	DENMARK	1430	2020	04

SEMAGLUTIDUM	RYBELSUS 7 mg	tablets	7 mg	NOVO NORDISK A/S	DENMARK	1430	2020	07
SEMAGLUTIDUM	RYBELSUS 14 mg	tablets	14 mg	NOVO NORDISK A/S	DENMARK	1430	2020	10
TIGECYCLINUM	TIGECYCLINE ACCORD 50 mg	powder for solution for infusion	50mg	ACCORD HEALTHCARE S.L.U.	SPAIN	1394	2020	01
TREPROSTINILUM	TREPULMIX 1 mg/ml	solution for infusion	1mg/ml	SCIPHARM SÀRL	LUXEMBURG	1419	2020	01
TREPROSTINILUM	TREPULMIX 2.5 mg/ml	solution for infusion	2.5mg/ml	SCIPHARM SÀRL	LUXEMBURG	1419	2020	02
TREPROSTINILUM	TREPULMIX 5 mg/ml	solution for infusion	5mg/ml	SCIPHARM SÀRL	LUXEMBURG	1419	2020	03
TREPROSTINILUM	TREPULMIX 10 mg/ml	solution for infusion	10mg/ml	SCIPHARM SÀRL	LUXEMBURG	1419	2020	04