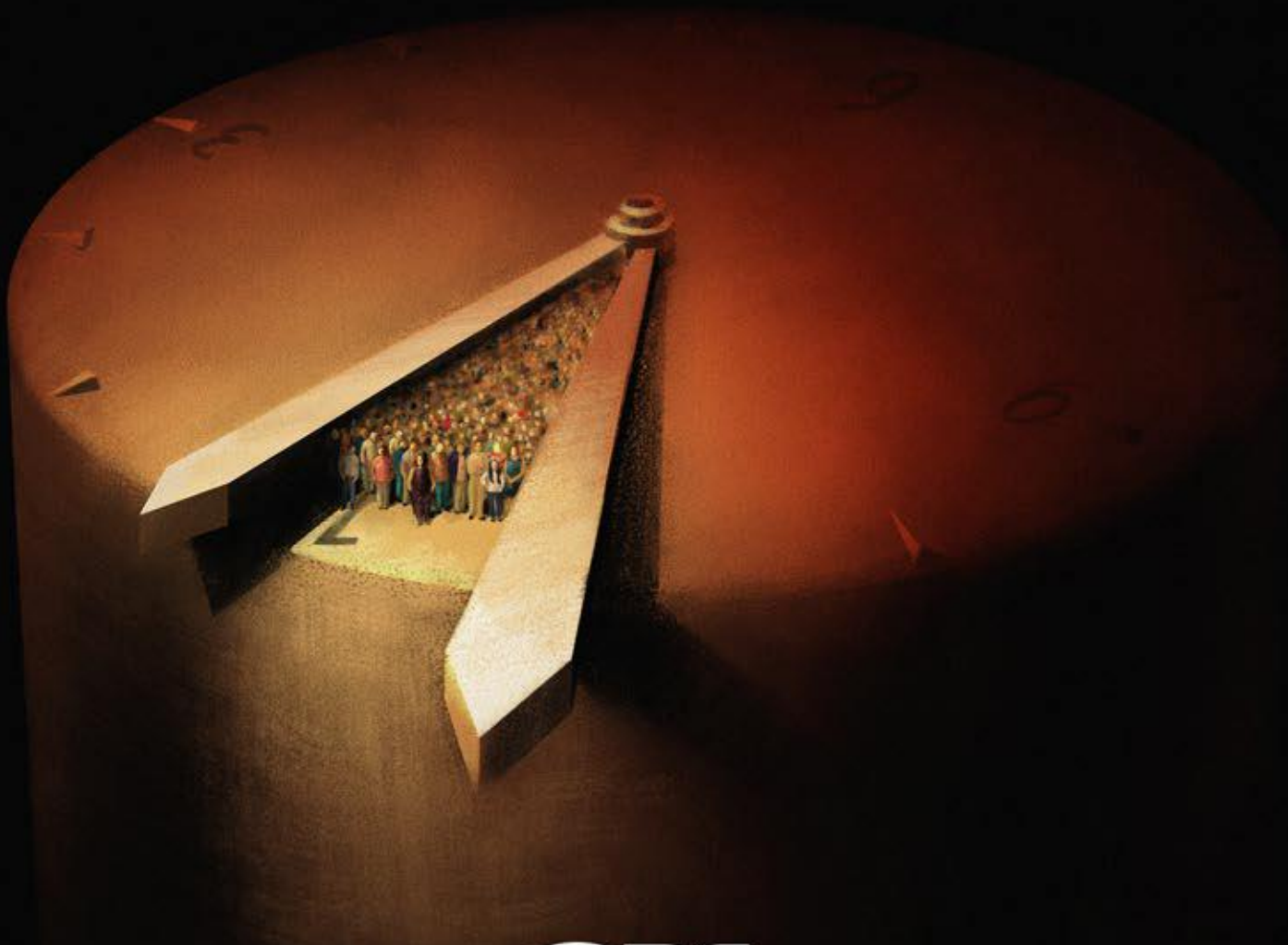
THE CRISIS OF ANTI-TB MEDICINES IN ROMANIA

ALERT REPORT

October 2017, Bucharest



Romanian Health Observatory

Stop TB Partnership ROMANIA

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SUMMARY

15 drugs essential to the treatment of tuberculosis are reported to have difficulties in procurement and availability.

PROBLEM

Romania is not capable of providing all the drugs that are essential to the treatment of tuberculosis, a contagious disease designated as a public health priority. Most drugs for drug-resistant tuberculosis are not available today to the Romanian patients under the programmes run by the Romanian Government.

International organisations provide the drugs essential to the treatment of a limited number of tuberculosis patients in Romania. The international funding allocated for this purpose will be exhausted in 2018, and at that point these patients will be left without medication if Romania is not able to take over the financing. At present, the Romanian Government is unable to fulfil its legal duties towards the patients.

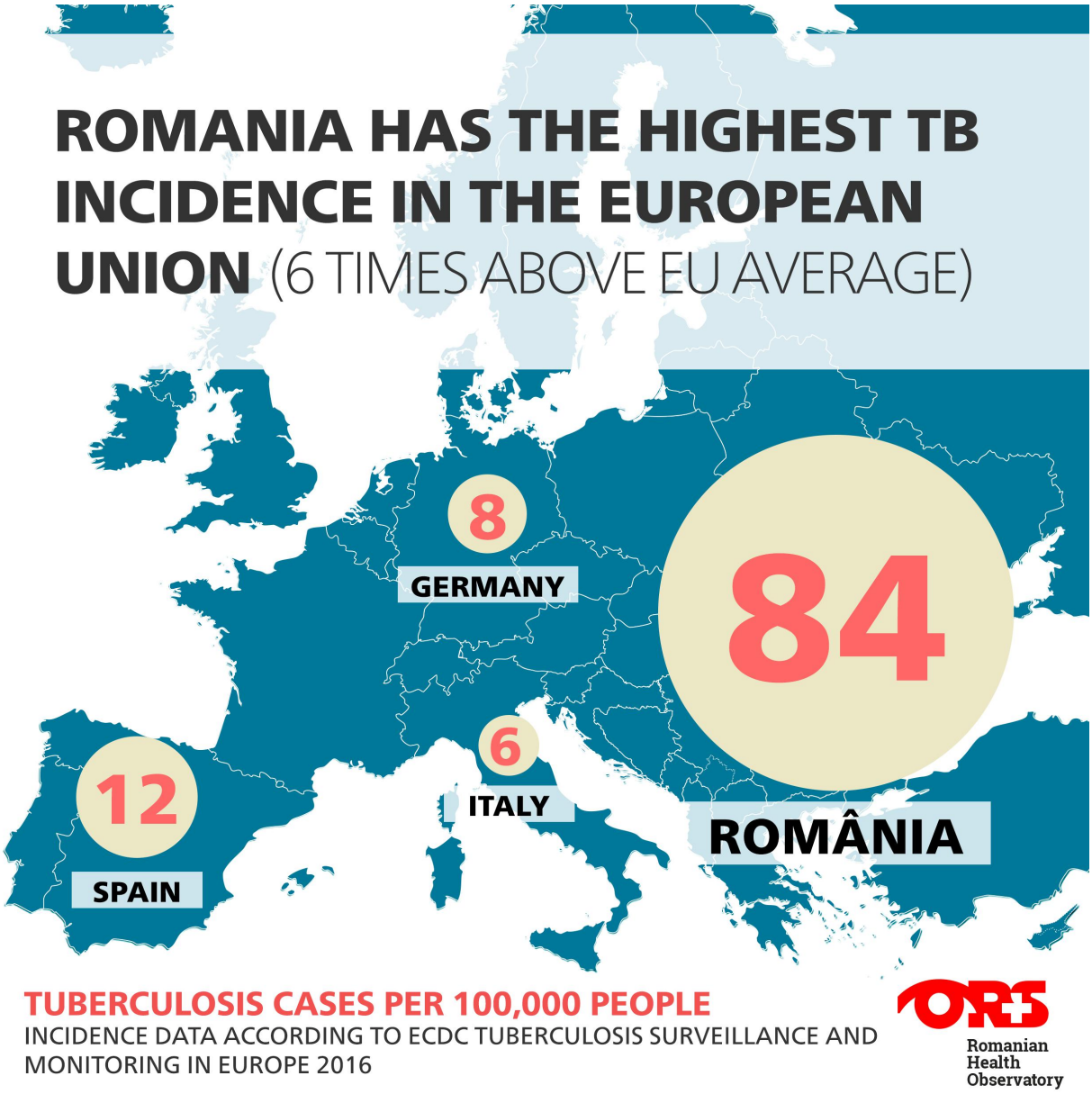
CAUSE

The absurd and contradictory legislation coupled with cumbersome bureaucracy block the patients' access to treatment which is vital for them.

EFFECT

There are deficiencies in terms of tuberculosis patients being cured – Romania has one of the lowest cure rates for drug-resistant tuberculosis in the world. The existing bureaucracy considerably hampers the therapeutic efforts of medical practitioners and makes it hard to limit the spreading of tuberculosis in the Romanian population.

> "A TB patient enrolled in internationally-funded programmes is a lot luckier than a patient treated under the programmes managed by the Romanian State."
>
> - Specialist physician at a Romanian hospital



Romania: overview of tuberculosis, a fully curable disease

- **21.167** tuberculosis patients in Romania in 2016 *
- **The lowest cure rate** in the EU **
- **1 of 4 cases** of tuberculosis diagnosed in the EU in 2015 are in Romania ***
- **1.055 people died** from TB in Romania in 2015 alone *
- **12.790 new cases and relapses** recorded in Romania in 2016 **

- People affected by TB mainly come from the young and active population [*]
- **Bucharest, Dolj, Iași, Bacău and Constanța:** the counties with the highest number of cases in Romania [*]
- Over **500 new drug-resistant tuberculosis cases** are detected annually. [**]
- According to World Health Organization estimates, 800-1000 new drug-resistant cases should be diagnosed annually in Romania. **The lack of the equipment and consumables necessary** for appropriate diagnosis leads to the detection of only 500 – 600 cases annually. [**]

> "Practically, today I have no treatment regimen available for resistant tuberculosis."
>
> - Specialist physician at a Romanian hospital, September 2017

The Romanian Government asserted in Government Decision (HG) no. 121/2015 that "Tuberculosis is a public health priority in Romania." Unfortunately, because of their passive approach, the authorities ignore this major problem, and fail to provide tuberculosis patients with "complete, continuous and correctly-administered treatment," which is an obligation stipulated in the legislation.

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[*] source: The "Marius Nasta" Institute of Pulmonology UATM-PNPSCT. TB Endemic – June 2017.
[**] source: The National Public Health Institute. TB situation analysis. 2017.
[***] source: European Centre for Disease Prevention and Control. Tuberculosis surveillance and monitoring in Europe, 2017.

Even more worrying is that by maintaining a contradictory legislation and an absurd bureaucracy, the Romanian authorities worsen the situation of tuberculosis patients and contribute to the increase, from year to year, of the pool of patients infected with drug-resistant tuberculosis (this phenomenon is noted even in the Romanian National Tuberculosis Control Strategy).

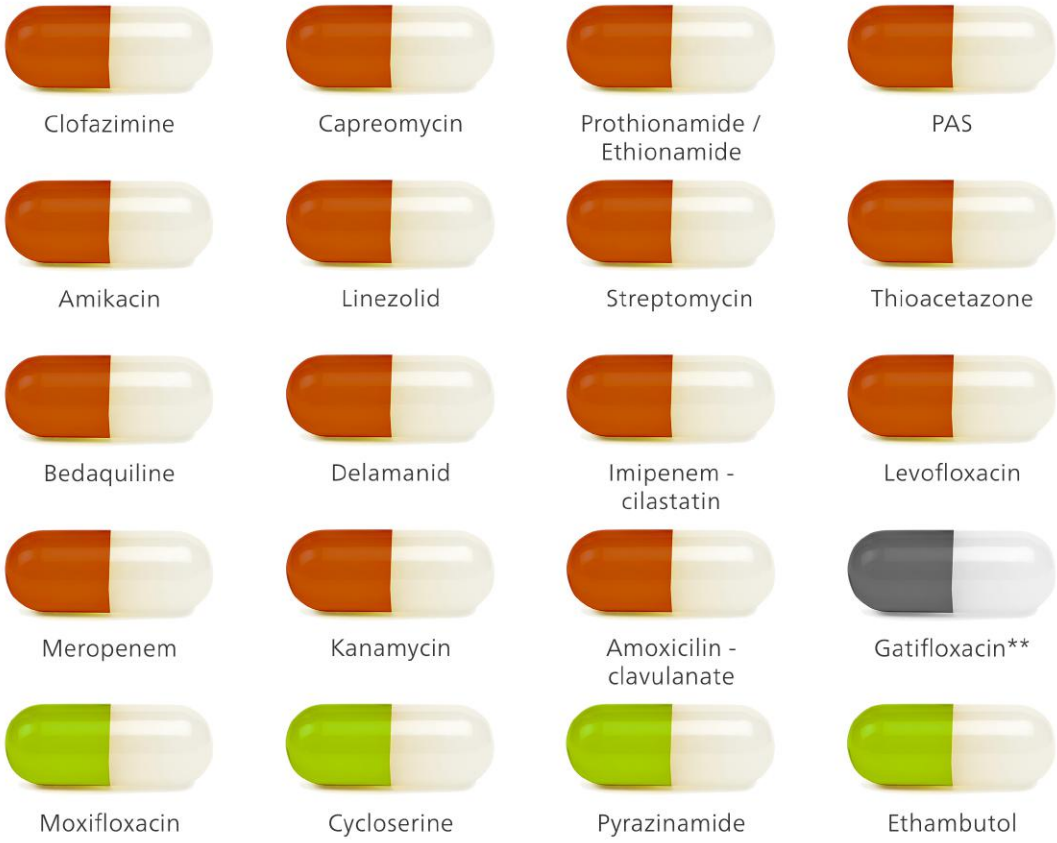
ESSENTIAL The anti-TB treatment consists of several drugs that have to be administered simultaneously. If the patient takes an incomplete anti-TB regimen, the bacterium will rapidly develop resistance to the treatment.

Of the 28 drugs analysed – mentioned as essential or necessary in the treatment of TB and drug-resistant TB according to the recommendations of the World Health Organization or of the Methodological Guidelines for the Implementation of the National Programme for the Prevention, Surveillance and Control of Tuberculosis in Romania – a significant number of **15 essential drugs are reported to show discontinuities/difficulties** in terms of supply caused by the legislative barriers existing in Romania. 3 other drugs recommended in the guidelines, but considered to have alternatives, are absent in Romania.

- Of the 20 drugs recommended by the World Health Organization for **drug-resistant** tuberculosis (MDR/XDR-TB), 15 are absent or their procurement is problematic in Romania.
- 8 drugs are not included on the list of drugs reimbursed by the Romanian State for the treatment of TB patients, although they are officially recommended by the World Health Organization for this disease (they are absent from the C2 list, the TB sub-programme, in HG 720/2008).
- 14 drugs, meaning half of those necessary, have not been assigned a reimbursement price, which makes it impossible for public institutions to procure them legally. This bureaucratic barrier blocks patient access to vital treatment that the state has undertaken to reimburse as a legal obligation (the drugs are not included on the required list in the Order of the Minister for Health OM) no. 1605/875/2014).

- For 14 drugs, the centralised procurement procedures were not organised either because of insufficient funds, or because of bureaucratic barriers; in 5 cases, the drugs may be provided to the patients legally **only** if, in addition to the tuberculosis diagnosis, they are also diagnosed with HIV.
- 10 drugs essential for the treatment of tuberculosis are brought in Romania using special needs authorisations, a laborious and lengthy procedure that should only be used in isolated and exceptional cases.
- 5 drugs do not have a marketing authorisation in Romania because the manufacturer is not interested in Romania for commercial reasons.

AVAILABILITY OF MULTIDRUG-RESISTANT TUBERCULOSIS MEDICINES* IN ROMANIA



* RECOMMENDED BY THE WORLD HEALTH ORGANIZATION ** GATIFLOXACIN (MISSING) IS INCLUDED IN THE WHO GUIDELINES, BUT IT IS NOT CONSIDERED ESSENTIAL BY THE ROMANIAN MEDICAL COMMUNITY

15 MEDICINES MISSING OR WITH PURCHASE PROBLEMS

4 MEDICINES AVAILABLE ON THE MARKET

ANTI-TB DRUGS IDENTIFIED AS HAVING A SUBSTANTIAL RISK OF DISCONTINUITY

Very high-risk group (Drugs with registration problems in Romania)

- Clofazimine
- Para-aminosalicylic acid (PAS)
- Capreomycin
- Prothionamide

Special case: the unavailability of Streptomycin, a drug of major importance for the treatment of tuberculosis.

High-risk group (drugs without reimbursement price and not included specifically in the section relating to the tuberculosis programme of the reimbursement list)

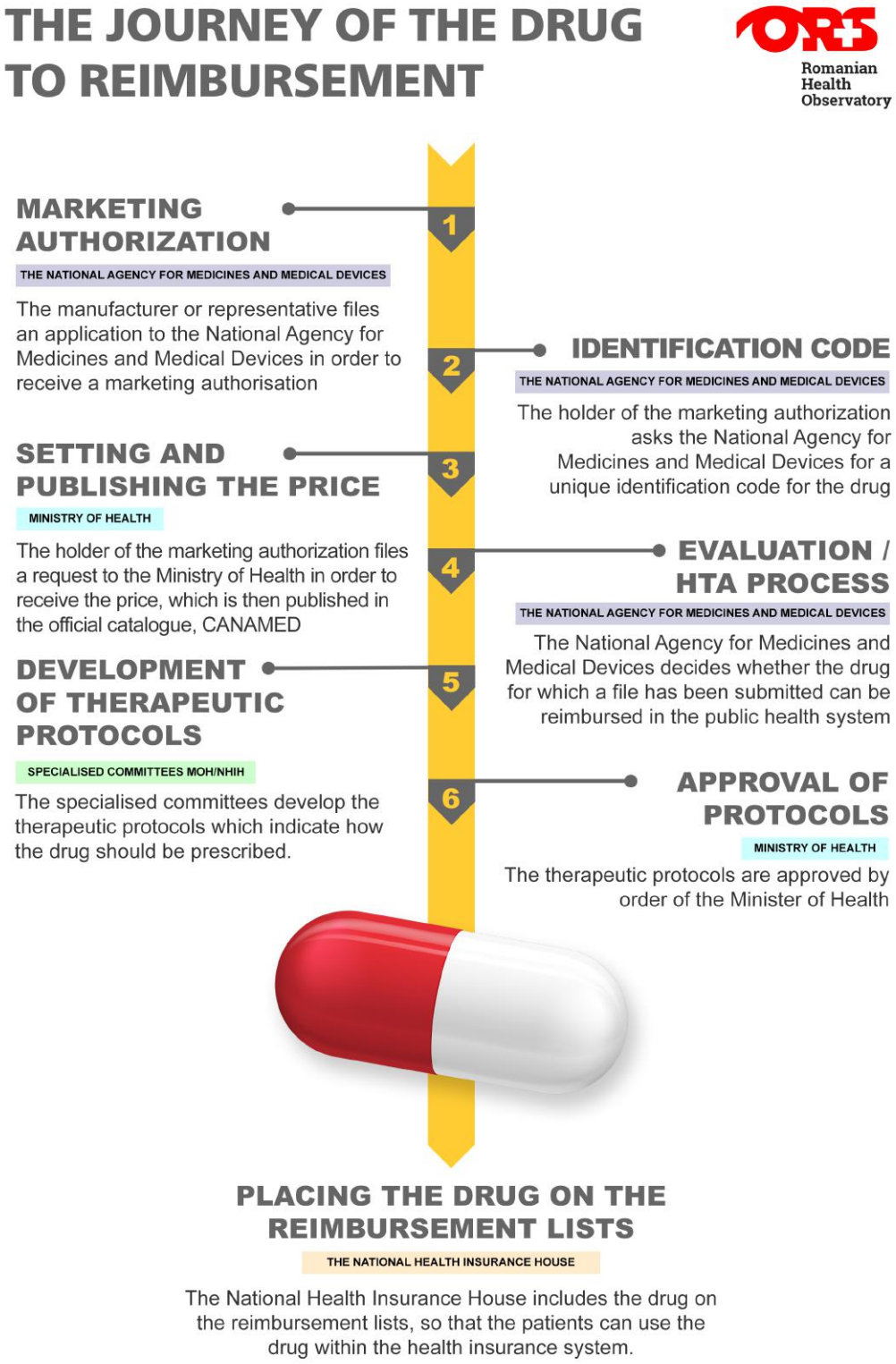
- Levofloxacin
- Linezolid
- Meropenem
- Amoxicillin with clavulanic acid
- Imipenem with cilastatin

Medium-risk group

- Kanamycin
- Rifabutin
- Delamanid

"I don't understand if this crisis is caused by ill intentions or by carelessness."

- Physician responsible for the treatment of a significant number of TB patients


THE JOURNEY OF THE DRUG TO REIMBURSEMENT
Romanian Health Observatory
MARKETING AUTHORIZATION
1
THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES
The manufacturer or representative files an application to the National Agency for Medicines and Medical Devices in order to receive a marketing authorisation
IDENTIFICATION CODE
2
THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES
The holder of the marketing authorization asks the National Agency for Medicines and Medical Devices for a unique identification code for the drug
SETTING AND PUBLISHING THE PRICE
3
MINISTRY OF HEALTH
The holder of the marketing authorization files a request to the Ministry of Health in order to receive the price, which is then published in the official catalogue, CANAMED
EVALUATION / HTA PROCESS
4
THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES
The National Agency for Medicines and Medical Devices decides whether the drug for which a file has been submitted can be reimbursed in the public health system
DEVELOPMENT OF THERAPEUTIC PROTOCOLS
5
SPECIALISED COMMITTEES MOH/NHIH
The specialised committees develop the therapeutic protocols which indicate how the drug should be prescribed.
APPROVAL OF PROTOCOLS
6
MINISTRY OF HEALTH
The therapeutic protocols are approved by order of the Minister of Health
PLACING THE DRUG ON THE REIMBURSEMENT LISTS
THE NATIONAL HEALTH INSURANCE HOUSE
The National Health Insurance House includes the drug on the reimbursement lists, so that the patients can use the drug within the health insurance system.

CAUSES OF THE LACK OF ESSENTIAL ANTI-TB DRUGS

All the drugs referred to below are recommended for the treatment of tuberculosis in the international guidelines drawn up by the World Health Organization.

1. A significant number of drugs which are essential for the treatment of tuberculosis[1] are not on the national reimbursement list in HG 720/2008, in the section dedicated to the sub-programme for the treatment of TB patients.

Harmful effect: None of these drugs may be procured through a centralized procedure by the Romanian State using the budget dedicated to the national public health programmes, which also include the treatment of tuberculosis. This is a serious barrier for the access of TB patients to drugs essential for their cure. The barrier is created and maintained by the Romanian authorities themselves.

Bureaucratic absurdity: The same drugs that are not included in the National Tuberculosis Prevention, Surveillance and Control Programme are included in the similar National HIV Programme. Practically, patients that are diagnosed with both HIV and TB are luckier than those who only have a TB diagnostic, because the latter do not have access to drugs necessary for their cure.

Another paradox is that because of the legislation governing the field, these drugs that are essential in the treatment of tuberculosis may not be financed from the budget allocated to the National TB Programme, but may be co-financed if brought in Romania using a special needs authorisation (SNA). However, the special needs authorisation is a complex

[1] *According to the World Health Organization guidelines*

and laborious bureaucratic procedure that takes at least 6 months (see the infographic below), and which should be used in exceptional cases, not as a rule.

The fact that the HG 720/2008 list dedicated to TB treatment is not correctly updated has led to a situation in which drugs that are no longer recommended in the treatment of TB, such as Ciprofloxacin, are included in the reimbursement, while essential drugs such as Clofazimine are not.

Practically, the Romanian State blocks the access of TB patients to essential medication by maintaining cumbersome and lengthy bureaucratic procedures.

Paradoxes: There are serious inconsistencies in the very wording of these legislative acts on which patients' lives depend. Different articles of Law no. 95/2006 or from the secondary legislation are not correlated and contradict each other.

For example, Section C2 of HG 720/2008 comprises the drugs intended, according to the section title, for patients "included in the national health programmes for curative purposes". However, Section C2 also includes national health programmes (for preventive purposes), as is the one for TB. The difference is important, because the two types of programmes are financed from different sources: the curative ones are financed from the funds of the National Health Insurance House, while the public health programmes are financed from the budget and from the funds of the Ministry of Health.

It must be noted that the Ministry of Health proposed amendments that remedy part of these legislative contradictions, which are included in a Government Ordinance put up for public debate in August 2017. By the time of the publication of this Report, the amendments proposed had not been approved by the Romanian Government.

2. Almost half of the drugs recommended by the World Health Organization as essential in the treatment of tuberculosis do not have a reimbursement price and therefore may not be legally procured by the authorities.

Harmful effect: In order for the authorities to be able to procure the drugs from the budget dedicated to national health programmes, the drugs must be assigned a reimbursement price, mentioned in OMS 1605/875/2014. Without this price, drugs cannot be bought, nor become available to patients.

Bureaucratic absurdity: Four drugs are in an illogical situation. They are included in the national lists that allow their reimbursement (HG 720/2008), but not on the list that establishes the reimbursement prices (OMS 1605/875/2014). Without their inclusion on both lists, the state cannot purchase these drugs through a centralised procurement procedure. **Examples of essential drugs included on the reimbursement list, but without reimbursement price:** Kanamycin, Para-aminosalicilic acid, Rifabutin, Capreomycin.

Practically, the absence from the list of reimbursement prices for anti-TB drugs creates a considerable barrier for the access of tuberculosis patients to vital treatments. This barrier is created by the Romanian state itself.

Paradoxes: One of the drugs that are important for patients with the severe form of drug-resistant tuberculosis, Prothionamide, was excluded in April 2017 from the list of reimbursement prices (it is no longer present in item 94 of the national tuberculosis programme of OMS 1605/875/2014). However, Prothionamide is maintained on the list that permits its reimbursement expressly to patients with drug-resistant tuberculosis (HG 720/2008). In the absence of a reimbursement price, it cannot be made available to patients. In Romania, there is no alternative to this treatment.

NUMBER	DATE OF PUBLICATION	AWARD DATE	OBJECT OF CONTRACT	FORM / CONCENTRATION	WINNER
167408	13.04.2016	27.09.2016	Cicloserinum	capsules 250 mg	Pharma S.A.
		27.09.2016	Isoniazidum	tablets 300 mg	Pharma S.A.
		27.09.2016	Protionamidum	tablets 250 mg	Pharma S.A.
		27.09.2016	Ofloxacinum	tablets 200 mg	Europharm Holding S.A.
		27.09.2016	Pyrazinamidum	tablets 500 mg	Pharma S.A.
		27.09.2016	Ethambutolum	tablets 250 mg	Imeco S.A.
		27.09.2016	Ethambutolum	tablets/tablets 400 mg	Pharma S.A.
		27.09.2016	Moxifloxacinum	tablets 400 mg	Farmexpert D.C.I. SRL
		27.09.2016	Rifampicinum	tablets 150 mg	Pharma S.A.
		27.09.2016	Claritromicinum	tablets 500 mg	Mediplus Exim S.R.L.
		27.09.2016	Prednisonum	tablets 5 mg	Imeco S.A.
		27.09.2016	Pyridoxinum	tablets 250 mg	Imeco S.A.
		27.09.2016	Isoniazidum	100 mg	Pharma S.A.
171358	11.11.2016	21.06.2017	Rifampicinum	capsules 300 mg	Pharma S.A. Mediplus Exim Farmexpert SRL
		21.06.2017	Rifampicinum+izoniazidum	capsules 300 + 150 mg	Pharma S.A. Mediplus Exim Farmexpert SRL
181968	23.09.2017	29.08.2017	Moxifloxacinum	IV solution 400mg/25ml	Fresenius Kabi
		29.08.2017	Imipenemum + Cilastatinum	IV powder 500mg/500mg	Mediplus Exim S.R.L.
		29.08.2017	Clarithromycinum	IV powder 500mg	Mediplus Exim S.R.L.
		29.08.2017	Linezolidum	IV solution 2mg/ml	Fildas Trading SRL
		29.08.2017	Meropenemum	IV powder 1000mg	Mediplus Exim S.R.L.
		29.08.2017	Meropenemum	IV powder 500mg	Mediplus Exim S.R.L.
		29.08.2017	Ciprofloxacinum	IV solution 100mg/10ml	Mediplus Exim S.R.L.
		29.08.2017	Amoxicillinum + Acidum Clavulanicum		Mediplus Exim S.R.L.
		29.08.2017	Ciprofloxacinum	IV solution 2mg/ml	Infomed Fluids SRL
		29.08.2017	Levofloxacinum	IV solution 5mg/ml	Fresenius Kabi Romania SRL

Table (source: Ministry of Health): Drugs necessary for TB treatment purchased through centralised procedure by the Ministry of Health in the period 2015 – 2017: in green, drugs that may be used (procured from TB-dedicated funds); in yellow, drugs that may not be used legally for the treatment of TB patients from funds dedicated to them.

3. A legislative provision very useful for tuberculosis patients is rendered useless by the passivity of Romanian authorities.

Harmful effect: At the beginning of 2017, the introduction of a very useful legislative amendment enabled all anti-TB drugs mentioned in the World Health Organization guidelines to automatically be accepted for reimbursement in Romania (OMS 487/2017) and, by way of consequence, to be included on the two required lists. However, one single drug, Delamanid, has benefitted from this provision so far (Decision no. 159/2017), being also introduced on the lists in question.

Bureaucratic absurdity: The drugs in question may benefit from this useful provision only if their manufacturers (the marketing authorisation holders) submit application for the assessment of the drug (HTA) to the National Agency for Medicines and Medical Devices.

According to the legislation, even in the absence of such an application, the National Agency for Medicines and Medical Devices may initiate the assessment of the drugs in question if they meet one of the criteria set out by the law. However, the legislation does not explicitly stipulate an obligation of Romanian authorities to carry out such an assessment if no manufacturer is interested, but there is a major public health interest. As a result, the current legislation creates an additional useless barrier for the access of patients to vital treatments.

Paradoxes: The fact that some of these drugs do not have the treatment of tuberculosis as indication (the so-called off-label drugs) is sometimes used as a bureaucratic argument against the need to change the legislation. In fact, there are anti-TB drugs that, despite being off-label, are included on all the lists that represent conditions necessary for reimbursement, such as Moxifloxacin. At the same time, other off-label drugs are not included on all the lists that represent conditions for reimbursement. There is no explanation for these differences.

4. Essential drugs for the treatment of a severe form of tuberculosis (MDR/XDR-TB) are not registered on the Romanian market.

Harmful effect: Essential drugs for patients with drug-resistant tuberculosis do not have a marketing authorisation in Romania and, as a result, cannot be procured by the Romanian health institutions. Clofazimine and Capreomycin are the most worrying examples because

they considerably influence the correct treatment of this type of patients. Authorisation applications must be submitted by the drug manufacturers, but this has not happened. In most cases, manufacturers/distributors invoke commercial reasons for their lack of interest in the Romanian market.

Pricing policies used by the Romanian authorities, coupled with a number of patients that does not guarantee profit, have transformed Romania into an unattractive market for companies that manufacture these essential drugs for the treatment of resistant tuberculosis.

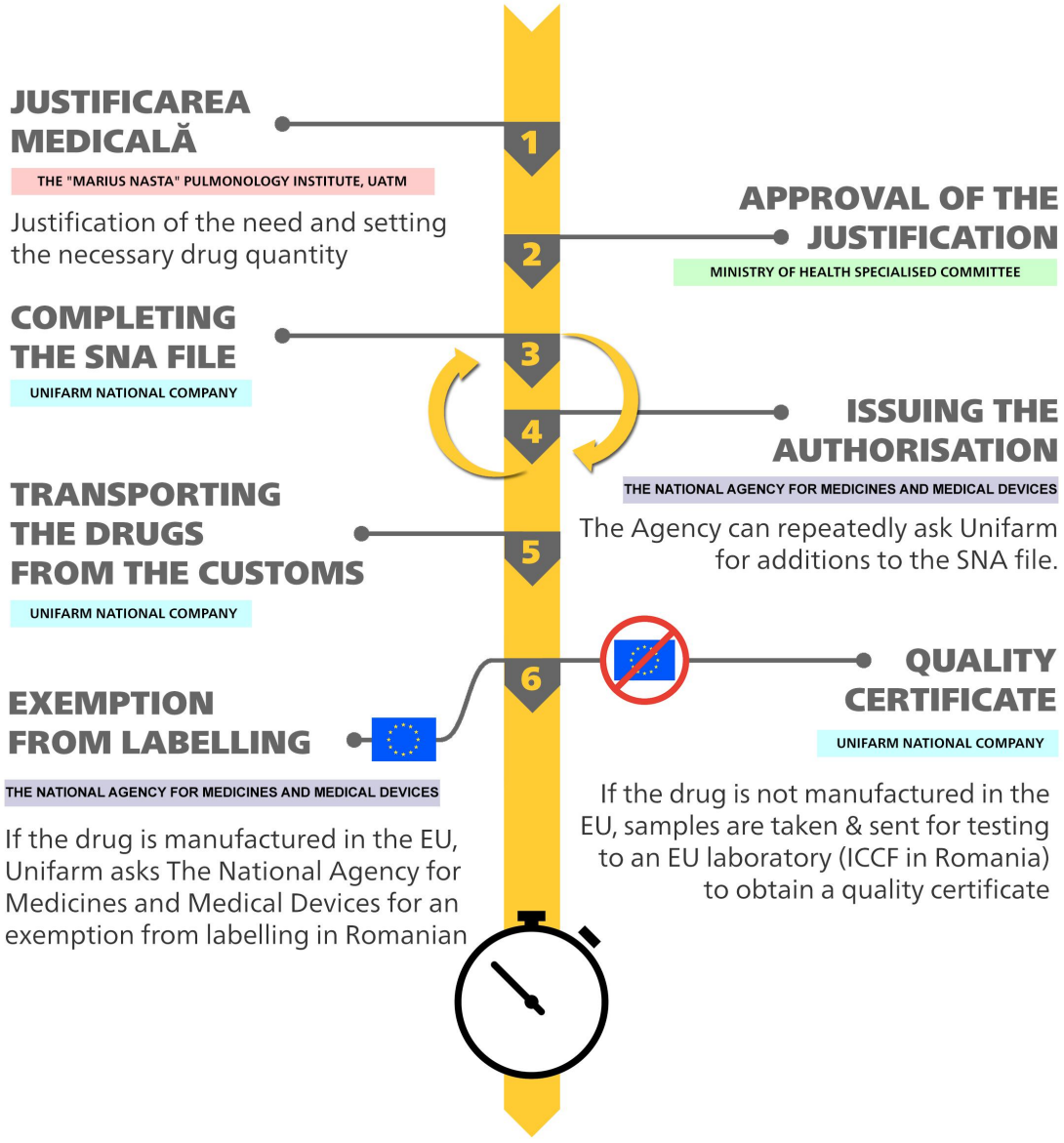
Bureaucratic absurdity: The drugs in this situation may be brought in Romania only through the issuance of a special needs authorisation. The legislation specifies that the issuance of special needs authorisations is also possible for drugs that are registered in Romania but cannot be obtained via the usual channels in a reasonable amount of time. This solution is a "temporary" one, as the legislation explicitly states.

At present, 10 drugs that are essential for the treatment of tuberculosis are brought in Romania using the special needs authorisation, which turned from a "temporary" solution into a permanent one. Drugs that are registered and drugs that are not registered in Romania, as well as drugs with indication for tuberculosis and drugs without (off-label) are brought in the country using such authorisations.

In the absence of coherent and consistent legislative solutions, a provision that was intended for exceptional cases has become the rule. This makes the procurement of TB drugs unpredictable, leaving it at the discretion of various decision-makers within state institutions and exposed to supply discontinuities.

Paradoxes: The procedure for obtaining a special needs authorisation (SNA) is very laborious, unpredictable and lengthy (see the infographic below). The file must contain a large number of documents, among which 5 different certificates the validity of which can expire before the special needs authorisation is granted, requiring their re-submission. The period for obtaining a special needs authorisation for tuberculosis drugs recommended by the World Health Organization is between 6 and 8 months.

OBTAINING THE SPECIAL NEEDS AUTHORISATION (SNA)



THE TREATMENT REACHES THE PATIENT 6 TO 8 MONTHS AFTER THE PROCESS HAS BEEN INITIATIED

CASE-BY-CASE ANALYSIS OF THE REASONS FOR THE ABSENCE OF ESSENTIAL ANTI-TB DRUGS

The group of first-line anti TB drugs essential for patients with drug-sensitive tuberculosis

- **Streptomycin**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
Yes	Yes	Yes	No

Status of the drug: it is recommended in the WHO guidelines and in the Romanian guidelines; it is authorised in Romania; it is included on the C2 list, the TB sub-programme; it is not procured by centralised procedure; it does not have special needs authorisation.

Reason for absence: it is no longer available in Romania since 2016 because there is no manufacturer of the active substance.

Solution: the granting of a special needs authorisation for the estimated need of 4000 patients.

- Rifampicin and Ethambutol – not available in injectable form.

- **Rifabutin**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
Yes	No	Unifarm	No

Status of the drug: it is recommended in the WHO guidelines and in the Romanian guidelines (as an alternative to Rifampicin); there is no manufacturer/distributor interested in registering this drug in Romania, the marketing authorisation holder being Unifarm, the state's distributor; it is included on the C2 list, the TB sub-programme; it is not procured by centralised procedure by the Romanian authorities; it has a special needs authorisation only for procurement from funds made available by international organisation.

Reason for absence: although it is included on the C2 list, the TB sub-programme, the drug has not been assigned a reimbursement price, therefore it cannot be legally procured by the Romanian authorities.

Solution: the assigning a reimbursement price and the organisation of a centralised procurement procedure.

The group of second-line anti-TB drugs essential in the treatment of MDR/XDR tuberculosis

- **Kanamycin**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
Yes	No	Yes	No

Status of the drug: it is recommended in the WHO guidelines and in the Romanian guidelines; it is authorised in Romania; it is included on the C2 list, the TB sub-programme; it is not procured by centralised procedure by the Romanian authorities; it has special needs authorisation only for procurement from funds made available by international organisations.

Reason for the absence: although it is included on the C2 list, the TB sub-programme, the drug has not been assigned a reimbursement price, therefore it cannot be legally procured by the Romanian authorities; unofficial sources claim that the drug was intentionally eliminated because of a price increase.

Solution: the assigning of a reimbursement price and the organisation of a centralised procurement procedure.

- **Amikacin**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
Yes (for MDR-TB)	Yes	Yes	No

Status of the drug: it is recommended in the WHO guidelines and in the Romanian guidelines; it is authorised in Romania; it is included on the C2 list, the TB sub-programme; it is not procured by centralised procedure; it does not have a special needs authorisation.

Reason for the absence: the contract for the centralised procurement was not signed because of the manufacturer's tax-related problems. As a result, hospitals may procure the drug directly, but not by using the Ministry of Health funds dedicated to the treatment of tuberculosis patients.

Solution: the organisation of a centralised procurement procedure.

- **Capreomycin**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
Yes (for MDR-TB)	No	No	No

Status of the drug: it is recommended in the WHO guidelines and in the Romanian guidelines; it is not authorised in Romania; it is included on the C2 list, the TB sub-programme; it is not procured by centralised procedure; it has a special needs authorisation only for procurement from funds made available by international organisations.

Reason for the absence: the product is not registered in Romania.

Solution: the application of the Cyprus clause, whereby a EU Member State may register a drug in the absence of an application for registration submitted by a private entity (see details in the chapter "Urgent Measures Necessary").

- **Prothionamide**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
Yes (for MDR-TB)	No	No	No (yes in 2016)

Status of the drug: it is recommended by the WHO guidelines and by the Romanian guidelines; it is no longer authorised in Romania; it is not included on the C2 list, the TB sub-programme; it was procured by centralised procedure in September 2016, it is no longer procured at present; it has a special needs authorisation only for procurement from funds made available by international organisations.

Reason for the absence: it was excluded without explanations from the reimbursement price list in April 2017, which makes it impossible to legally procure the drug by centralised procurement procedure.

Solution: the application of the Cyprus clause, whereby a EU Member State may register a drug in the absence of an application for registration submitted by a private entity (see details in the chapter "Urgent Measures Necessary"). The re-assigning of a reimbursement price.

> "This drug is no longer available today because of purely bureaucratic reasons. Nobody watched out for the approvals not to expire."
>
> - Specialised physician at a Romanian hospital

- **Levofloxacin**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
No (Yes in the HIV programme)	No	Yes	No

Status of the drug: it is recommended in the WHO guidelines and in the Romanian guidelines; it is authorised in Romania; it is not included on the C2 list, the TB sub-programme, although it appears in the HIV sub-programme; it has a special needs authorisation only for procurement from funds made available by international organisations.

Reason for the absence: it cannot be legally procured by centralised procedure by the Romanian authorities for treating tuberculosis patients because it is not included on the C2 list; it is an off-label drug.

Solution: the inclusion on the C2 list, the TB sub-programme, through the application of OMS 487/2017 and the assigning of a reimbursement price for centralised procurement.

- **Para-aminosalycilic acid (PAS)**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
Yes (for MDR-TB)	No	No	No

Status of the drug: it is recommended in the WHO guidelines and in the Romanian guidelines; it is no longer authorised in Romania; it is included on the C2 list, the TB sub-programme; it is not procured by centralised procedure; it has a special needs authorisation only for the procurement from funds made available by international organisations.

Reason for the absence: although it is included on the C2 list, the TB sub-programme, the drug has not been assigned a reimbursement price, therefore it cannot be legally procured by the Romanian authorities; no mamufacturer is interested in marketing it in Romania.

Solution: the application of the Cyprus clause, whereby a EU Member State may register a drug in the absence of an application for registration submitted by a private entity (see details in the chapter "Urgent Measures Necessary").

- **Meropenem**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
No (Yes in the HIV programme)	No	Yes	No

Status of the drug: is recommended in the WHO guidelines and in the Romanian guidelines; it is authorised in Romania; it is not included on the C2 list, the TB sub-programme, although it is present in the HIV sub-programme; it is not procured by centralised procedure; it does not have a special needs authorisation.

Reason for the absence: it cannot be legally procured by centralized procedure by the Romanian authorities for the treatment of TB patients because it is not included on the C2 list, the TB sub-programme; it is an off-label drug.

Solution: the inclusion on the C2 list, the TB sub-programme through the application of OMS 487/2017 and the assigning of a reimbursement price for centralised procurement.

- **Bedaquiline**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
Yes	Yes	Yes	No

Status of the drug: it is recommended in the WHO guidelines and in the Romanian guidelines; it is authorised in Romania; it is included on the C2 list, the TB sub-programme; it is not procured by centralised procedure; it does not have a special needs authorisation.

Reason for the absence: although all the legal conditions are met for it to be procured by centralised procedure from the funds dedicated to the treatment of tuberculosis, Bedaquiline is not procured by centralised procedure, the argument invoked informally being the absence of funds. Another cause is the medical recommendation that this drug be administered only together with Linezolid. Linezolid is currently not available (see below), therefore the procurement of Bedaquiline would be useless for tuberculosis patients.

Solution: the deployment of the necessary funds and of the complete treatment regimen for tuberculosis.

- **Linezolid**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
No (Yes in the HIV programme)	No	Yes	No

Status of the drug: it is recommended in the WHO guidelines (considered a first-line drug for drug-resistant tuberculosis) and in the Romanian guidelines (where it is considered by some specialists to have a risk of causing certain resistant forms); it is authorised in Romania; it is not included on the C2 list, the TB sub-programme, although it is present in the HIV sub-programme; it is not procured by centralised procedure; it has a special needs authorisation only for procurement from funds made available by international organisations.

Reason for the absence: it cannot be legally procured by centralised procedure by the Romanian authorities for the treatment of TB patients because it is not included on the C2 list, the TB sub-programme; it is an off-label drug.

Solution: the inclusion on the C2 list, the TB sub-programme, through the application of OMS 487/2017 and the assigning of a reimbursement price for centralised procurement.

- **Delamanid**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
Yes	Yes	Yes	No

Status of the drug: it is recommended in the WHO guidelines and in the Romanian guidelines; it is authorised in Romania; it is included on the C2 list, the TB sub-programme; it is not procured by centralised procure; it does not have a special needs authorisation.

Reason for the absence: although it is included on the C2 list in the TB sub-programme and although it has a reimbursement price assigned, which is why it can be legally procured by centralised procedure, the drug is not being procured. The informal reason invoked is the absence of funds.

Solution: the organisation of a centralised procurement procedure.

- **Clofazimine**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
No	No	Unifarm	No

Status of the drug: it is recommended in the WHO guidelines and in the Romanian guidelines; no manufacturer/distributor is interested in registering this drug in Romania, the marketing authorisation holder being Unifarm, the state's distributor; it is not included on the C2, the TB sub-programme; it is not procured by centralised procurement procedure; it has a special needs authorisation only for procurement from funds made available by international organisations.

Reason for the absence: the manufacturer of this drug is not interested in supplying the quantity required in Romania, because of commercial reasons; the drug is not included on the C2 list, the TB sub-programme, therefore it may cannot be legally procured by centralised procedure by the Romanian authorities; it is an off-label drug.

Solution: the application of the Cyprus clause, whereby a EU Member State may register a drug in the absence of an application for registration submitted by a private entity (see details in the chapter "Urgent Measures Necessary") and the inclusion on the C2 list, the TB sub-programme, through the application of OMS 487/2017

- **Amoxicillin with clavulanic acid**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
No (Yes, for the HIV programme)	No	Yes	No for TB Yes for HIV programme

Status of the drug: it is recommended in the WHO guidelines and in the Romanian guidelines; it is authorised in Romania; it is not included on the C2 list, the TB sub-programme, although it is present in the HIV sub-programme; it is not procured by centralised procedure from the funds dedicated to tuberculosis patients, although it is being procured by centralised procedure for another purpose; it does not have a special needs authorisation.

Reason for the absence: it cannot be legally procured by centralised procedure by the Romanian authorities for the treatment of TB patients because it is not included on the C2 list, the TB sub-programme; it is an off-label drug.

Solution: the inclusion on the C2 list, the TB sub-programme, through the application of OMS 487/2017 and the assigning of a reimbursement price for centralised procurement.

- **Imipenem with cilastatin**

Present in the C2 list, TB sub-programme	Has reimbursement price	Has marketing authorisation	Is procured by centralised procedure
No (Yes for HIV programme)	No	Yes	No for TB Yes for HIV programme

Status of the drug: it is recommended in the WHO guidelines and in the Romanian guidelines; it is authorised in Romania; it is not included on the C2 list, the TB sub-programme, although it is present in the HIV sub-programme; it is not procured by centralised procedure from the funds dedicated to tuberculosis patients, although it is procured by centralised procedure from funds used for other purposes; it does not have a special needs authorisation.

Reason for the absence: it cannot be legally procured by centralised procedure by the Romanian authorities for the treatment of TB patients because it is not included on the C2 list, the TB sub-programme; it is an off-label drug.

Solution: inclusion on the C2 list, the TB sub-programme, through the application of OMS 487/2017 and the granting of a reimbursement price for centralised procurement.

Fixed combinations of anti-TB drugs recommended by the World Health Organization for increasing patient compliance with the treatment

These combinations are requested by physicians and recommended by WHO experts because they are useful for increasing patient adherence to the treatment and for making the treatment easier. The following combinations are not available in Romania:

- **Isoniazid + Rifampicin + Ethambutol** – necessary for an estimated number of 1,000 patients
- **Isoniazid + Rifampicin + Ethambutol + Pyrazinamide** – necessary for an estimated number of 2,000 patients.

SUSTAINABLE LONG-TERM SOLUTIONS FOR SOLVING THE ANTI-TB DRUG CRISIS

"Decision-makers within the Ministry and within the National Agency for Medicines and Medical Devices understand that there is a problem and that the law is stupid, but nobody dos anything to change it."

- Public servant in a governmental institution with responsibilities in TB prevention and treatment

Using the "Cyprus clause" and maintaining the obligation to include anti-TB drugs recommended by the World Health Organization on the national reimbursement list (the current HG 720/2008).

It is urgently necessary to automatically include in the legislation mentioned above all the drugs recommended in the World Health Organization Guidelines for the treatment of MDR/XDR tuberculosis. This is already possible as a result of the approval of Order no. 487/2017 amending and supplementing OMS 861/2014.

In order for the beneficial effects of this Order to be fully felt, it is necessary to either have requests for assessment (HTA) for anti-TB drugs submitted to the National Agency for Medicines and Medical Devices, or for the ANMDM to act on own-initiative.

For drugs without marketing authorisation in Romania, it is necessary to apply Article 126a of Directive 2001/83/EC (the so-called "Cyprus clause"), which states that "In the absence of a marketing authorisation or of a pending application for a medicinal product authorised in another Member State in accordance with this directive, a Member State may for justified public health reasons authorise the placing on the market of the said medicinal product."

This clause has already been used by other EU Member States such as Cyprus, Portugal, Latvia or Poland.

The Romanian legislation provides for the possibility of activating the "Cyprus clause" in Article 883 of Law no. 95/2006, which also identifies the National Agency for Medicines and Medical Devices as the responsible institution. At the time this Report was being

drafted, unlike the EU Member States referred to above, Romania had not used the "Cyprus clause."

The argument that this is not possible for off-label drugs is not valid because there are already two off-label drugs included on the list of drugs that are reimbursed and have a reimbursement price within the national tuberculosis programme: Moxifloxacin and Ofloxacin.

Amending the legislative regime governing the reimbursement of drugs financed under national public health programmes.

It is necessary to amend the Health Law no. 95/2008 in order to exempt drugs financed under the national public health programmes from the condition of being included on the national reimbursement lists set out in HG 720/2008, which would also exempt them from going through the current HTA assessment and reimbursement price circuit for reimbursement.

In addition to this exemption, the Ministry of Health should be able to procure by centralised procedure the drugs set out in the national public health programmes, by:

- Allowing suppliers with authorisation in a EU Member State as well to participate in the procurement procedures for the drugs included in the national public health programmes;
- Establishing clear criteria for including the drugs provided under the national public health programmes based on the existing international guidelines.

The authors of this Report consider that this solution, although simpler from a legislative point of view, may open the door for potential arbitrary measures unless very strict evaluation criteria are defined for the drugs that are to be financed under the national public health programmes.

URGENT MEASURES NECESSARY FOR SOLVING THE DRUG CRISIS

- **For drugs without marketing authorisation in Romania**

For drugs that do not have a marketing authorisation in Romania it is urgently necessary to apply Article 126a of Directive 2001/83/EC (the so-called "Cyprus clause").

- **For drugs not included on the national list for reimbursement under the sub-programme dedicated to TB patients**

For drugs that are not included on the national list for reimbursement under the National Tuberculosis Sub-Programme, it is necessary to urgently include them on the reimbursement list. This is legally possible provided that the HTA procedure is facilitated for the drugs included in the World Health Organization Guidelines, and this facilitation has already been introduced in the legislation by OMS 487/2017.

In order to handle the situations where there is no supplier willing to submit a HTA application, followed by the inclusion on the national reimbursement list, the National Agency for Medicines and Medical Devices must initiate the assessment of the drugs in question on own initiative.

- **For drugs without reimbursement price in the national health programmes**

For the drugs not included on the list of reimbursement prices, it is necessary to urgently update the legislative act setting out these reimbursement prices.

- **Drugs that are "off-label" in Romania but are recommended by the World Health Organization for the treatment of tuberculosis**

The "off-label" use of drugs means the use of the drugs outside the information approved through the marketing authorisation (MA) in relation to the therapeutic indications, recommended dosage, route of administration, pharmaceutical form, and age group. It is a relatively common medical practice. In accordance with the Romanian legislation, drugs used "off-label" do not fall under the scope of regulations covering drugs used for resolving special needs.

Example

Moxifloxacin is a drug that is recommended for use in the treatment of resistant tuberculosis (MDR/XDR TB) in the World Health Organization guidelines[2], but in Romania the use of Moxifloxacin for this indication is considered to be "off-label." Nevertheless, Moxifloxacin is included on the national reimbursement list in the tuberculosis sub-programme, it was procured by centralised procedure using the Ministry of Health funds dedicated to TB patients and, at the same time, has been issued a special needs authorisation for procurement using international funds.

Therefore, the "off-label" capacity of a drug recommended by the World Health Organization for the treatment of tuberculosis should not represent an impediment for its reimbursement and procurement from public funds dedicated to the national TB programme.

Moreover, to avoid drug crises and ensure the continuity of centralised drug procurement procedures, the Ministry of Health must urgently implement the following measures:

1. The legal obligation for the centralised procurement procedures to be completed before the end of the framework contract in force, in order to avoid drug supply discontinuities.
2. The estimation of the budget needs for at least 2 years for centralised anti-TB drug procurement.
3. The appointment of a person within the Ministry of Health having the sole duty of prospecting the market for the organisation of centralised procurement procedures for the national public health programmes, and of monitoring the stocks/consumption of drugs in real time.
4. The inclusion in the framework contracts for centralised procurement of the supplier obligation to ensure the supply of the contracted drugs, otherwise the supplier being obliged to pay significant penalties.

[2] WHO treatment guidelines for drug-resistant tuberculosis, 2016 update. October 2016 revision.

APPLIED METHODOLOGY

The mapping of the drugs evaluated in the Report uses the World Health Organization guidelines (WHO treatment guidelines for drug-resistant tuberculosis – October 2016 Revision) and the Methodological Guidelines for the Implementation of the National Tuberculosis Prevention, Surveillance and Control Programme (Ministry of Health, the "Marius Nasta" Institute of Pulmonology – 2015).

For obtaining the information needed for this Report, we conducted interviews with 12 persons: physicians with competence in the treatment of tuberculosis, patients, representatives of the authorities, pharmaceutical policy experts, and representatives of the pharmaceutical industry. All the interviews were conducted anonymously in order to generate an evaluation as open as possible.

Quality documentary sources used in the drawing up of this Report:

- Guidelines for treatment of drug-susceptible tuberculosis and patient care – 2017 Update. World Health Organization.
- GLC-Europe Monitoring Mission to Romania (Askar Yedilbayev, rGLC-Europe, 2016)
- Short Term Assessment TB Supply Chain, Romania (Peter Evans, WHO Regional Office for Europe, 2016).
- Raport cu privire la evaluarea cadrului legal și a reglementărilor specifice privind achiziția de medicamente antituberculoase, evaluarea barierelor curente (*Report on the evaluation of the legal framework and specific regulations on the procurement of anti-TB drugs, the evaluation of current barriers*) (Popa Cristian George).
- Endemie TB – iunie 2017 (*TB Endemics – June 2017*) (Chiotan Domnica, Cioran Nicoleta, the "Marius Nasta" Institute of Pulmonology, 2017).
- Analiza de situație TBC 2017 (*TB Situation Analysis 2017*) (Lungu Elena, Muntianu Emilia Catalina, Cotea Iuliana Daniela, Paiu Daniela, the National Public Health Institute, 2017).

The consultation of the primary and secondary legislation in the field, as well as the accessing of the data existing in the Public Procurement Electronic System and in other public databases have informed the conclusions and recommendations of this Report.