Application for the inclusion of isoniazid for intravenous use (addition – new formulation/strength of existing medicine) in the WHO Model List of Essential Medicines and Model List of Essential Medicines for Children, section 6.2.4 as a first-line drug for the treatment of tuberculosis in severely ill patients and those who have absorption disorders as a lifesaving possibility to receive proper anti-tuberculosis treatment

Name of applicant(s): CU Communicable Diseases Intensive Care Association "Incure", Ukraine
www.incure.info
Contact person:
dr Tetiana Sprynsian, tel: +380665134849, email: info@incure.info

**1. Summary statement of the proposal for inclusion, change or deletion.**

Tuberculosis (TB) is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS). TB is caused by the bacillus Mycobacterium tuberculosis, which is spread when people who are sick with TB expel bacteria into the air; for example, by coughing. The disease typically affects the lungs (pulmonary TB) but can also affect other sites (extrapulmonary TB).

Every year, 10 million people fall ill with tuberculosis (TB). Despite being a preventable and curable disease, 1.5 million people die from TB each year – making it the world's top infectious killer [1].

TB is the leading cause of death of people with HIV and also a major contributor to antimicrobial resistance, which means the urgent need in additional efforts to study the main reasons of treatment failure and additional efforts to save those 1.5 million lives per year.

Among all TB deaths, 77,2% of patients die during intensive phase of treatment and 36.4% of patients die in the first 10 days of the treatment, according to recent studies. [9] That means, severe TB patients are in the blind zone of the standard TB care and require additional treatment efforts, for example hospitalization and using anti-TB preparations with immediate action, such as intravenous drugs instead of tablets.

Isoniazid is one of the most effective chemotherapeutical components that is present in main treatment regimens of drug-susceptible tuberculosis recommended by WHO.

Isoniazid, the hydrazide of isonicotinic acid, is highly bactericidal against replicating tubercle bacilli. It is rapidly absorbed and diffuses readily into all fluids and tissues. The plasma half-life, which is genetically determined, varies from less than one hour for fast acetylators to more than three hours for slow acetylators. Isoniazid is largely excreted in the urine within 24 hours, mostly as inactive metabolites. According to WHO guidelines 2017, Isoniazid is normally taken orally but may be administered intramuscularly or intravenously to critically ill people. [2]

The EML and EMLc already contain preparations of oral Isoniazid. This application proposes IV isoniazid for the core list of WHO Model List of Essential Medicines and Model List of Essential Medicines for Children, as a lifesaving medicine for the following categories:

1. Patients with severe forms of tuberculosis with poor outcomes, requiring intensive treatment (Miliary TB [34,35], caseous pneumonia[36], TB meningitis [37], TB sepsis [38-39], TB pericarditis[42]).

2. Patients with acute or chronical gastrointestinal diseases, or patients with reduced absorption rates of oral forms (malabsorption in PLWH [15-19]).

3. Patients with severe comorbidities: HIV/TB, diabetes/TB [44], etc.

4. Patients that are unable (unconscious patients in ICU or in coma) or unwilling to take drugs in periods of depression or due to acute manifestations of altered mental condition. [14]

Target regimen profiles for TB treatment: rifampicin-susceptible, rifampicin resistant and pan-TB treatment regimens, published in 2016 by WHO state that IV formulations should be reserved for cases of severe forms of disease, such as CNS TB or TB sepsis for both susceptible and resistant forms of tuberculosis. Currently, intravenous isoniazid is not available on most of the markets. The absence of IV isoniazid in both EML and EMLc prevents national and international TB programs from purchasi ng needed quantity of IV forms.

## 2. Name of the focal point in WHO supporting the application

Dr Ernesto Jaramillo, MDR-TB Policy & Innovations department, World Health Organization Geneva, Switzerland

Bernadette Cappello, Secretariat, Essential Medicines List, World Health Organization Geneva, Switzerland

## 3. Name of the organizations consulted and supporting the application

International Union Against Tuberculosis and Lung Disease (The Union), National institute of phthisiology and pulmonology named after F.G. Yanovsky NAMS of Ukraine,

CU Communicable Diseases Intensive Care Association “Incure”, Ukraine,

Higher State Educational Establishment "Bukovinian State Medical University", Ukraine,

Novosibirsk TB Research Institute (NTRI), Russian Federation,

Universitas Padjadjaran Department of Pharmacology therapy, Indonesia, Clinical Research Unit and Institute of Biomedicine/Center for Global Health,

Universitatea de Medicină şi Farmacie „Grigore T. Popa” Iaşi, Romania. "Marius Nasta" Pneumoftiziology Institute, Romania

## 4. International non-proprietary name of the medicine e (INN, generic name) of the medicine

ISONIAZID

ATC code: J04AC01

## 5. Formulation proposed for inclusion

**Formulation:** powder for injections/solution for injections,

**Strength(s):** 300 mg, 500 mg and 900 mg/vial

**Indication:** treatment of susceptible tuberculosis in combination with other first-line drugs

**Addition –** new formulation/strength of existing medicine

The EML and EMLc already contain preparations of oral Isoniazid. This application is for the additional inclusion of powder for injections/solution for injections Isoniazid 300 mg, 500 mg, 900 mg.

300 mg of Isoniazid is maximum recommended daily dose and it can be used as a fast and well-tolerated remedy for severe cases of tuberculosis. According to different sources (FDA, AHFS monograph, guidelines), isoniazid can be used up to 900 mg daily in intermittent regimen thrice a week. [2-6]

## 6. Whether listing is requested as an individual medicine or as representative of a pharmacological class

Listing is requested as an individual medicine. According to WHO Guidelines, first line drugs for the treatment of susceptible tuberculosis (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol) are widely available in their oral forms, however are not yet presented as I.V. preparations.

## 7. Treatment details (requirements for diagnosis, treatment and monitoring).

According to WHO guidelines [6], IV formulations should be reserved for cases of severe forms of disease, such as central nervous system (CNS) TB or TB sepsis. [7]

I.V. isoniazid is also recommended for use by American Thoracic Society. [8] I.e. IV isoniazid should be considered for the patients with severe forms of the disease (TB meningitis, TB sepsis), patients with acute or chronical gastrointestinal diseases, or patients with reduced absorption rates of oral forms (malabsorption in PLWH [17-21]). Patients that are unable (unconscious patients in ICU or in coma [44]) or unwilling to take drugs in periods of depression or due to acute manifestations of altered mental condition. [16] Patients with severe comorbidities: HIV/TB, diabetes/TB [44], etc.

**Necessary conditions for intravenous infusion of anti-tuberculosis preparations:**

- Placement of an implanted port or peripherally inserted central catheter (PICC) line (a non-tunneled venous catheter)
- Using intravenous (IV) therapy to infuse injectable drugs for 30 to 60 minutes, 5 days per week
- Direct observation of ingestion of prescribed oral anti-TB drugs
- Monitoring for adverse reactions and reporting these to the supervising physician
- Extensive patient education and support to help ensure adherence

IV therapy may be given via an implanted port (placed surgically under the skin, usually in the chest) or by PICC line (placed in the forearm and threaded into the superior vena cava). Both methods have their advantages and disadvantages, and the choice is usually made by the physician based upon the needs of the patient. [40]

## 8. Information supporting the public health relevance Epidemiological information on disease burden

Globally, an estimated 10.0 million (range, 8.9–11.0 million) people fell ill with TB in 2019, a number that has been declining very slowly in recent years. There were an estimated 1.2 million (range, 1.1–1.3 million) TB deaths among HIV-negative people in 2019 (a reduction from 1.7 million in 2000), and an additional 208 000 deaths (range, 177 000–242 000) among HIV-positive people (a reduction from 678 000 in 2000). Men (aged under 15 years) accounted for 56% of the people who developed TB in 2019; women accounted for 32% and children (aged under 15) for 12%. Among all those affected, 8.2% were people living with HIV. [1]

Among all TB deaths, 77,2% of patients die during intensive phase of treatment and 36.4% of patients die in the first 10 days of the treatment, according to recent studies. The fact of death from tuberculosis is usually confirmed in Intensive care unit (ICU). [8]

**Assessment of current use**

According to WHO guidelines for susceptible tuberculosis treatment, both pulmonary and extra-pulmonary forms of drug susceptible TB have to be treated with daily dosing of 6-month rifampicin-based regimen 2HRZE/4HR, with the only difference that adjuvant corticosteroid therapy should be considered in case of TB meningitis.

According to the last WHO Model List of Essential Medicines (2019), only oral forms of first line anti-tuberculosis drugs are included [9].

**Target population(s)**

Several studies show that there is a decrease in the functional absorptive area of the intestine in TB patients, which would explain the reduced serum concentrations of anti-tuberculosis drugs. Patients with malabsorption syndrome don't get the minimum therapeutic level of anti-tuberculosis drugs, therefore such patients have to be treated or with higher doses of these drugs, what will cause higher level of adverse reactions from gastrointestinal system, or another dosage form should be considered. [8-11], [25-33]

Although most HIV-infected patients with tuberculosis (TB) respond well to rifampin-based anti-mycobacterial drug regimens [17], recent reports suggest that malabsorption of anti-mycobacterial drugs occurs in selected HIV-infected patients, particularly those with advanced HIV infection [18-22].

Up to 70% of admissions to ICU with active tuberculosis have acute respiratory failure (ARF) and require mechanical ventilation. [12-13] Mortality rate for such patients according to a retrospective cohort study in Brazil is up to 80%. [10] The causes of ARF in most of the cases are miliary lesions in lungs.

Other causes of TB death are Mycobacterium tuberculosis sepsis in immunocompromised patients [39-40], tuberculous pericarditis [42] and tuberculous meningitis [37].

Tuberculous meningitis (TBM) is one of the most devastating manifestations of extra-pulmonary tuberculosis (TBEP) and is associated with severe morbidity and high mortality up to 80% of cases. [14]

## 9. Review of benefits: summary of comparative effectiveness in a variety of clinical settings.

Intravenous first line drugs for TB treatment are not available in most of the countries. However, IV forms ensure the quickest and the most complete access of the medicinal substance to the foci of TB infection.

Intravenous anti-TB drugs are essential for treating different categories of TB patients, including those with severe disseminated and gastrointestinal TB for whom oral anti-TB agents alone might not be effective. In some cases, this is caused by quick decomposition of the drugs during their relatively slow intake from the gastrointestinal tract and, in others, by the impossibility of increasing the dose. In the case of intravenous administration, the drugs are easily absorbed, which leads to the creation of higher concentrations in the infected tissues. [15]

## 10. Review of harms and toxicity: summary of evidence on safety.

Isoniazid efficiency/safety profile has been studied during long term period and despite it's great anti-mycobacterial activity it can cause severe hepatotoxicity. Although drug-induced liver injury (DILI) caused by different drugs is somewhat different, the clinical characteristics of INH-induced liver injury are fairly typical for idiosyncratic DILI and include malaise, fatigue, nausea and vomiting. The duration of therapy before manifestation of jaundice can vary between 1–25 weeks with an average of 12 weeks. Fever affects on average 20% of the patients and eosinophilia is present in up to 15% of the affected individuals. In most cases, liver injury is asymptomatic and is only detected by measuring markers of hepatocyte injury such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). This is especially true for mild cases of liver injury, which occur in up to 20% of patients treated with the drug. However, in most patients, liver function returns to normal despite continued treatment with the drug, a phenomenon referred to as 'adaptation' by hepatologists. Severe liver injury is seen in up to 1% of the patients. Elevations in ALT and AST can start as early as 1 week and sometimes as late as 9 months after starting treatment with INH. However, in more than half of the patients an ALT increase occurs between 1–6 months. The abrupt increase in ALT that leads to liver failure is idiosyncratic in nature and is not clearly related to the duration of treatment, the dose of the drug, fever or eosinophil count [2] When liver injury is identified, the first line of treatment is to stop the drug and monitor the patient for recovery. In most cases patients recover. However, rechallenge of patients with more severe liver injury can result in a rapid onset of symptoms (within hours) and is contraindicated. Histological characteristics of severe INH-induced liver injury include hepatocellular injury with multi-lobular necrosis and a mononuclear cell infiltrate, which is generally indistinguishable from viral hepatitis. Steatosis is unusual in INH-induced liver injury. However, during active TB treatment, when INH is given in combination with other agents such as ethambutol, pyrazinamide and rifampicin (RMP), there have been reported cases of steatosis and cholestatic liver injury 7-9. Prolonged treatment with INH can also lead to a lupus-like autoimmune reaction with the presence of antinuclear antibodies, which occurs in up to 20% of the patients. [3] Unfortunately there is no published information about specific side effects of isoniazid due to iv route of administration, it is assumed that all side effects may be similar to those that occur with prolonged infusions - inflammation and pain at the catheter insertion site, the risk of infection and thrombosis, but all these phenomena should be studied in a special study. However, a small study indicated that long-term infusions with isoniazid and rifampicin did not produce specific route-of-administration side effects. [45] There is a small study describing possibility to decrease side effects related by using iv route of administration of 2$^{nd}$-line anti-TB drugs in MDR-TB patients, such as pain in the place of injection and phlebitis, by using port-catheter for intensive intravenous chemotherapy. [46]

## 11. Summary of available data on comparative cost and cost- effectiveness within the pharmacological class or therapeutic group.

There is no shown evidence in pharmacoeconomic convenience of IV isoniazid , considering following facts:

1) Low effectiveness of oral isoniazid on severe forms of tuberculosis.

2) Rare presence of IV isoniazid on most of the world markets, because of the

absence in EML and EMLc.

According to available online data on the prices, we suppose that injectable dosage form of ethambutol can be more expensive than the oral form.
In Ukraine iv isoniazid 500 mg is about $ 0.03-0.05 / vial,
In Kazakhstan iv isoniazid 500 mg is about $ 0.6-1/ vial.
In Uzbekistan iv isoniazid 500 mg is about $ 0.05-0.1/ vial.
In Russian Federation iv isoniazid 500 mg is about $ 0.04-0.08/ vial.
In UK iv isoniazid 50 mg\2 ml is registered but there is no information about price per vial.
Median Price for oral form of Isoniazid 300 mg is 0.019 - 0.02/tab. But it shouldn't be considered as an alternative drug, because oral forms cannot provide the same benefits for people affected by severe forms of tuberculosis.

Another point is that the appearance of intravenous isoniazid in the list of EML and EMLc will stimulate the manufacturers to produce i.v. isoniazid and the concurrence will decrease the prices for the treatment course.

## 12. Summary of regulatory status of the medicine

The US Food and Drug Administration (FDA) approved one IV Isoniazid 100 mg/ml in 2005.

Injectable Isoniazid is available in Italy, country under EMA regulation, Ukraine, Kazakhstan, Uzbekistan, Russian Federation.

## 13. Availability of pharmacopoeia standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

Isoniazid reference standards are available according to BP, IP, USP, EP.

## 14. References.

1. WHO, Global tuberculosis report 2020
2. Guidelines for treatment of drug-susceptible tuberculosis and patient care 2017 UPDATE Annex 6 ESSENTIAL FIRST-LINE ANTITUBERCULOSIS DRUGS, WHO, 2017
http://www.who.int/tb/publications/2017/tb_guidelines2017_annex6_en_v4.pdf?ua=1

3. Isoniazid monograph

https://www.drugs.com/monograph/isoniazid.html

4. https://www.drugs.com/condition/tuberculosis-latent.html

5. https://www.drugs.com/condition/tuberculosis-active.html

6. WHO/HTM/TB/2016.16 Target Regimen Profiles for TB Treatment, Treatment of Tuberculosis: Guidelines. 4th edition Geneva: World Health Organization

7. American Thoracic Society; CDC; Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep. 2003 Jun 20;52(RR-11):1-77. Erratum in: MMWR Recomm Rep. 2005 Jan 7;53(51):1203. Dosage error in article text. PubMed

8. Simonovska L, Trajcevska M, Mitreski V, Simonovska I. The causes of death among patients with tuberculosis; European Respiratory Journal Sep 2015, 46 (suppl 59) PA2713; DOI: 10.1183/13993003.congress-2015.PA2713

9. WHO model list of essential medicines, 2019

10. Pinheiro, Valéria G. F., Ramos, Lysiane M. A., Monteiro, Helena S. A., Barroso, Elizabeth C., Bushen, Oluma Y., Façanha, Mônica C., Peloquin, Charles A., Guerrant, Richard L., & Lima, Aldo A. M.. (2006). Intestinal permeability and malabsorption of rifampin and isoniazid in active pulmonary tuberculosis. Brazilian Journal of Infectious Diseases, 10(6), 374- 379.

https://dx.doi.org/10.1590/S1413-86702006000600003\

11. Kuzhko MM, Butov DO, Hulchuk NM, Avramchuk OV, Protsyk LM, et al. (2015) Clinical Case of Using Intravenous Forms of AntiTuberculosis Drugs to Improve the Treatment Efficiency of Tuberculosis in Patients with Malabsorption Syndrome. J Pulm Respir Med 5: 269. doi:10.4172/2161- 105X.1000269

12. Frame RN, Johnson MC, Eichenhorn MS, Bower GC, Popovich J Jr. Active tuberculosis in the medical intensive care unit: a 15-year retrospective analysis. Crit Care Med. 1987 Nov;15(11):1012-4

13. Silva DR, Menegotto DM, Schulz LF, Gazzana MB, Dalcin PT: Mortality among patients with tuberculosis requiring intensive care:a retrospective cohort study. BMC Infect Dis 2010, 10: 54. 10.1186/1471-2334-10-54

14. Efsen AM, Panteleev AM, Grint D, Podlekareva DN, Vassilenko A, Rakhmanova A, et al. TB Meningitis in HIV-Positive Patients in Europe and Argentina: Clinical Outcome and Factors Associated with Mortality . BioMed research international. 2013;2013:373601

http://dx.doi.org/10.1155/2013/373601

15. Metushi, I., Uetrecht, J., and Phillips, E. (2016) Mechanism of isoniazid- induced hepatotoxicity: then and now. Br J Clin Pharmacol, 81: 1030–1036. doi: 10.1111/bcp.12885.

16. Mason PH, Sweetland AC, Fox GJ, Halovic S, Nguyen TA, Marks GB. Tuberculosis and me ntal health in the Asia-Pacific. Australas Psychiatry. 2016 Dec;24(6):553-555. Epub 2016 May 20. Review. PubMed PMID: 27206468; PubMed Central PMCID: PMC5332205.

17. Alwood K, Keruly J, Moore-Rice K, Stanton DL, Chaulk PC, Chaisson RE. Effectiveness of supervised intermittent therapy for tuberculosis in HIV- infected patients, AIDS , 1994, vol. 8 (pg. 1103-8)

18. Berning SE, Huitt GA, Iseman MD, Peloquin CA. Malabsorption of antituberculosis medications by a patient with AIDS, N Engl J Med , 1992, vol. 327 (pg. 1817-8)

19. Peloquin CA, MacPhee AA, Berning SE. Malabsorption of antimycobacterial medications, N Engl J Med , 1993, vol. 329 (pg. 1122-3)

20. Patel KB, Belmonte R, Crowe HM. Drug malabsorption and resistant tuberculosis in HIV-infected patients, N Engl J Med , 1995, vol. 332 (pg. 336- 7)

21. Peloquin CA, Nitta AT, Burman NJ, et al. Low antituberculosis drug absorption in patients infected with human immunodeficiency virus, Ann Pharmacother , 1996, vol. 30 (pg. 919-23)

22. Gordon SM, Horsburgh CRJr, Peloquin CA, et al. Low serum levels of oral

antimycobacterial agents in patients with disseminated Mycobacterium avium complex disease, J Infect Dis , 1993, vol. 168 (pg. 1559-62)

23. Todoriko L.D., Pidverbetska O.V., Popovich M.G. Aspects of diagnosis of malabsorption syndrome in patients with tuberculosis. Conducting tactics / Medicus. – 2015. – №1. – P.69-70.

http://scimedicus.ru/d/743528/d/spisok-avtorov-medicus-(-1-(1)- yanvar).pdf

24. Todoriko L.D., Pidverbetska O.V. Clinical features of the drug susceptible, multi drug resistant and HIVassociated pulmonary tuberculosis depending on the degree of colon dysbiosis / Science and Education a New Dimension. Natural and Technical Sciences, IV (9), Issue: 83, 2016. – P. 64-67. http://seanewdim.com/published-issues.html

25. Todoriko L.D., Pidverbetska O.V. The condition of colon microbiocenosis in patients with pulmonary tuberculosis depending on the sensitivity spectrum of Mycobacterium tuberculosis and in patients with HIV/TB comorbidity / Tuberculosis, Lung Diseases, HIV infection.-2015.-№.3.-P.39-

44. http://tubvil.vitapol.com.ua/svizhij_nomer.php?nid=22

26. Todoriko L.D., Pidverbetska O.V. Evaluation of the absorption ability of the small intestine in patients with lungs TB and with a different profile of drug resistance of Mycobacterium TB / Infectious diseases. - 2015.-№3.P.65-68. https://ojs.tdmu.edu.ua/index.php/inf-patol/index

27. Todoriko L.D., Pidverbetska O.V. Intestinal microbiocenosis in patients with pulmonary tuberculosis, depending on the variant of pharmacoresistance before treatment / Actual Infectology. – 2015. – № 4(9). – P. 62-65. http://www.mif-ua.com/archive/article/42083

28. Todoriko L.D., Pidverbetska O.V. Optimization etiotropic and pathogenetic treatment of patients with primary diagnosed sensitive tuberculosis in consider of the functional condition of the intestine / Tuberculosis, Lung Diseases, HIV infection.-2016.-№.2.-C.56-62. http://tubvil.vitapol.com.ua/svizhij_nomer.php?nid=25

29. Todoriko L.D., Pidverbetska O.V., Besedinska A.V. Features of the organization of nuclear chromatin of epithelial cells of the small and large intestine in patients with pulmonary tuberculosis / Reports of Morphology (Vinnytsia National Medical University named after NI Pirogov). – 2016. – T.22, №1. – 68-70.

https://www.vnmu.edu.ua/downloads/other/visnik_morf_22(1).pdf

30. Todoriko L.D., Pidverbetska O.V. Features of the functional state of the intestine in patients with pulmonary tuberculosis, depending on the sensitivity spectrum of Mycobacterium tuberculosis / Bukovinian Medical Herald Journal – 2016. – № 2 (78). – P. 166-168. https://www.bsmu.edu.ua/files/BMV/BMV-2016-20-02%2878%29/41.pdf

31. Todoriko L.D., Pidverbetska O.V., Pidverbetskiy O.Ia., Slivka V.I. Absorption activity of the small intestine in patients with TB/HIV / International scientific and practical journal " RECIPE". – 2018. – Annex 2018 (Materials I Congress of Phthisiatricians and Pulmonologists of the Republic of Belarus "Modern directions of development of respiratory medicine and phthisiology") – P. 248-250. https://elibrary.ru/title_about.asp?id=28384

32. Todoriko L.D., Pidverbetska O.V., Kuzhko M.M., Sprinsyan T.A., Yeremenchuk I.V., Semyaniv I.A. Evaluation of the effectiveness of treatment of susceptible tuberculosis with a low rate of absorption

and malabsorption syndrome when administered intravenously with anti - tuberculosis drugs / International scientific and practical journal " RECIPE".– 2018. – Annex 2018 (Materials I Congress of Phthisiatricians and Pulmonologists of the Republic of Belarus "Modern directions of development of respiratory medicine and phthisiology") – P. 251-253. https://elibrary.ru/title_about.asp?id=28384

33. Todoriko L.D., Pidverbetska O.V., Yeremenchuk I.V., Semyaniv I.A. Characteristic of the functional state of the intestine at multidrug-resistant pulmonary tuberculosis / International scientific and practical journal " RECIPE". – 2018. – Annex 2018 (Materials I Congress of Phthisiatricians and Pulmonologists of the Republic of Belarus "Modern directions of development of respiratory medicine and phthisiology") – P. 260-262. https://elibrary.ru/title_about.asp?id=28384

34. Mbaave, Tsav & Achinge, G.I & Obekpa, S.A. (2016). Cryptic Miliary (Disseminated) Tuberculosis: A Case Report. IOSR Journal of Dental and Medical Sciences. 15. 84-86. 10.9790/0853-150758486.

35. Mert A, Arslan F, Kuyucu T, et al. Miliary tuberculosis: Epidemiologicaland clinical analysis of large-case series from moderate to low tuberculosis endemic Country. Medicine (Baltimore). 2017;96(5):e5875.

36. Evelina Lesnic, Olga Caraiani, Vasile Zlepca. Features and treatment outcome in caseous pneumonia. European Respiratory Journal 2012 40: P2600;

37. Anne Marie W. Efsen, Alexander M. Panteleev, Daniel Grint, et al., “TB Meningitis in HIV-Positive Patients in Europe and Argentina: Clinical Outcome and Factors Associated with Mortality,” BioMed Research International, vol. 2013, Article ID 373601, 9 pages, 2013. https://doi.org/10.1155/2013/373601.

38. Bridges, Debbie A. et al. Severe Tuberculosis Sepsis in an Immunocompetent Patient. The American Journal of Medicine, 2006: Volume 119 , Issue 3 , e11 - e14

39. G. E. Thwaites, N. D. Bang, N. H. Dung et al., Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. The New England Journal of Medicine, vol. 351, no. 17, pp. 1741–1751, 2004.

40. New Jersey Medical School National Tuberculosis Center. Outpatient Infusion Therapy for Multidrug-Resistant Tuberculosis: A Practical Guide. 2004: (inclusive pages).

41. http://www.stoptb.org/gdf/drugsupply/catalogue.asp

42. Faisal F. Syed, Bongani M. Mayosi, A Modern Approach to Tuberculous Pericarditis, Progress in Cardiovascular Diseases, Volume 50, Issue 3, 2007, Pages 218-236, ISSN 0033-0620, https://doi.org/10.1016/j.pcad.2007.03.002.

43. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis. 2009;9(12):737-46.

44. Tatar D, Senol G, Kirakli C, Edipoglu O, Cimen P. Contributing factors to mortality rates of pulmonary tuberculosis in intensive care units. J Chin Med Assoc. 2018;81(7):605-10..

45. Koestner JA, Jones LK, Polk WH, Sawyers JL. Prolonged use of intravenous isoniazid and rifampin. DICP. 1989;23(1):48-50.

46. Cherenko SO, Lytvynenko NA, Reva OA, Khmel OV, Veremeenenko RA, Pogrebna MV, et al. Safety and efficiency of the port-catheter for intensive intravenous chemotherapy in patients with multi-drug resistant tuberculosis and extensively drug-resistant tuberculosis. Infusion & Chemotherapy. 2018(1):19-24.