MINISTRY OF HEALTH
Palackého náměstí 375/4 128 01 Prague 2

Prague, 7 April 2020

Ref. No.: MZDR 13360/2020-3/OLZP

MZDRX019T6YJ

DECISION

The Ministry of Health, as the competent administrative authority pursuant to Section 11(o) of Act No 378/2007, on pharmaceuticals and on the amendment of certain related laws (hereinafter referred to as the "Act on Pharmaceuticals"), as amended, has decided on the following measure:

In the interest of protecting public health in relation to the current spreading of the causative agent of COVID-19 disease, the SARS-CoV-2 coronavirus, and in order to ensure the availability of medicinal products needed for the provision of medical care, the Ministry of Health, in accordance with Section 8(6) of the Act on Pharmaceuticals,

temporarily permits

the distribution, dispensing and use of the non-registered human medicinal product

HYDROXYCHLOROQUINE-SULFAAT TEVA 200 MG coated tablets (hydroxychloroquine sulphate), 30X200 MG

Producer: Merckle GmbH, Ludwig-Merckle-Str. 3, 89143 Blaubeuren, Germany,

the exterior and interior packaging of which is in the Dutch language (hereinafter the "medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA").

The following conditions are stipulated for the distribution, dispensing and use of the medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA:

1 **The medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA is designated for treating patients in the Czech Republic with proven COVID-19 infection, exclusively within the framework of hospitalisation.** Use in this case also applies to the provisioning of the patient with the necessary quantity of the medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA upon concluding hospitalisation or when transferring the patient to another healthcare services provider pursuant to Section 5(8)(a)(2) of the Act on Pharmaceuticals.

2. The medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA will be supplied

Electronic signature- 7 April 2020
Signature author's certificate:
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by distributors only to pharmacies which supply inpatient care providers.

3. The distribution of the medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA in the Czech Republic is ensured by:

4.

- **Teva Pharmaceuticals CR, s.r.o.,** registered office Radlická 3185/1 c, 150 00 Prague 5, Company ID No 25629646 (hereinafter referred to as "Teva Pharmaceuticals CR, s.r.o.") for the workplaces:
  - *Fakultní nemocnice Královské Vinohrady, Šrobárova 1150/50, 100 34 Prague 10,*
  - *Institut klinické a experimentální medicíny, Vídeňská 1958/9, 140 21 Prague 4,*
  - *Fakultní nemocníce v Motole, V Úvalu 84, 150 06 Prague 5,*
  - *Všeobecná fakultní nemocníce v Praze, U Nemocnice 499/2, 128 08 Prague 2,*
  - *Fakultní nemocníce Ostrava, 17. listopadu 1790/5, 708 52 Ostrava-Poruba,*
  - *Fakultní nemocníce Plzeň, Edvarda Beneše 1128/13, 305 99 Plzeň-Bory / alej Svobody 80, 304 60 Plzeň-Lochotín,*
  - *Fakultní nemocnice Olomouc, I. P. Pavlova 185/6, 779 00 Olomouc,*
  - *Fakultní nemocnice Hradec Králové, Sokolská 581, 500 05 Hradec Králové - Nový Hradec Králové,*
  - *Fakultní nemocnice Brno, Jihlavská 20, 625 00 Brno,*
  - *Thomayerova nemocnice, Vídeňská 800, 140 59 Prague 4 - Krč,*
  - *Nemocnice Jihlava, příspěvková organizace, Vrchlického 59, 586 33 Jihlava,*
  - *Fakultní nemocnice u sv. Anny v Brně, Pekařská 53, 656 91 Brno,*
  - *Nemocnice České Budějovice, a.s., B. Němcové 585/54, 370 01 České Budějovice,*
  - *Krajská nemocníce T. Bati, a. s., Havlíčkovo nábřeží 600, 762 75 Zlín,*
  - *Nemocníce Pardubického kraje, a.s., Kyjevská 44, 532 03 Pardubice,*
  - *Krajská zdravotní, a.s., Sociální péče 3316/12a, 400 11 Ústí nad Labem,*
  - *Nemocnice Na Bulovce, Budínova 67/2, 180 81 Prague 8 - Libeň,*
  - *Nemocnice Na Homolce, Roentgenova 37/2, 150 30 Prague 5.*
- **PHOENIX lékárenský velkoobchod, s.r.o.,** registered office K pérovně 945/7, 102 00 Prague 10 - Hostivař, Company ID No 453 59 326 (hereinafter referred to as "PHOENIX") for:
  - *other inpatient care providers.*

5. The distributor will submit a summary of the product characteristics for HYDROXYCHLOROQUINE-SULFAAT TEVA in the Czech language together with the delivery.
6. **The dispensing of the medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA requires a doctor's prescription (request).** The product can be dispensed only at the workplace of the given inpatient care provider ensuring the treatment of patients hospitalised with proven COVID-19 disease.
7. Healthcare services providers are ordered to ensure the **patient's informed consent** (or that of the legal guardian) to the use of the non-registered medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA.
8. The attending physician is ordered to report any negative side effects in accordance with Section 93b(1) of the Act on Pharmaceuticals, and any other negative side effects which occur in connection with the administration of the non-registered medicinal product, in the same manner as per Section 93b(1) of the Act on Pharmaceuticals.

This measure is effective for 8 months from the date of its posting on the official notice board of the Ministry of Health.

Justification:

On 26 March 2020, the Ministry of Health called on the State Drug Control Institute (hereinafter referred to as the "Institute") to submit an expert opinion pursuant to Section 8(6) of the Act on Pharmaceuticals, concerning non-registered medicinal products which contain the active substance *hydroxychloroquine.*

On 3 April 2020, the Ministry of Health received the expert opinion from the Institute, dated 3 April 2020, Ref. No sukl86212/2020, for the medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA. In terms of the decisive facts in the part of its opinion entitled *subject of request,* the Institute stated that because the quantity of the registered medicinal product PLAQUENIL 200MG TBL FLM 60, SÚKL code: 0054424, registration number 25/209/00-C, holder of marketing authorisation: sanofi-aventis, s.r.o., Prague, Czech Republic (hereinafter referred to as the "medicinal product PLAQUENIL") cannot cover the expected increased demand for medicinal products containing the active substance *hydroxychloroquine,* especially with regard to the adverse development of the epidemiological situation related to COVID-19 disease, it is necessary to ensure the availability of another medicinal product which contains this active substance.

The medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA should serve to cover the increased demand and be used to treat patients with COVID-19 disease. With regard to the fact that the medicinal product HYDROCHLOROQUINE-SULFAAT TEVA is registered in a European Union Member State, the Institute considers its quality and safety adequately proven. The effectiveness of the product for the treatment of COVID-19 disease has not yet been sufficient proven, and its use is thus based on the document *Recommended procedure - Specific treatment of adult patients with COVID-19 infection (version 1/270320),* which is the outcome of an assessment of pharmacotherapy options for patients with COVID-19, and which was created based on cooperation between specialised medical societies of the Czech

Medical Association of Jan Evangelista Purkyně (Society of Infectious Medicine, Czech Society of Anaesthesiology, Resuscitation and Intensive Medicine, Society for Transfusion Medicine), the COVID Clinical Group of the Ministry of Health, and the Institute (hereinafter referred to as the "Recommended procedure for treating COVID-19"). In the conclusion of its opinion, the Institute stated that in the case of the medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA, which is registered in another European Union Member State, the situation is the procurement of a medicinal product for treating a serious health condition. The Institute recommended permitting the use of the medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA whilst complying with the conditions it stipulates.

Upon assessment of the expert materials and given the expert opinion of the Institute, the Ministry of Health states the following:

In connection with the global spread of SARS-CoV-2 coronavirus, which causes COVID-19 disease, there is currently high demand for certain medicinal products, which either reduce the symptoms of the given disease or may be expected to be beneficial in treating COVID-19 disease, although these medicinal products are registered for the treatment of other diseases. These medicinal products include medicinal products which contain the active substance *hydroxychloroquine.* The effectiveness of *hydroxychloroquine* in treating COVID-19 disease has not yet been sufficiently proven, and its use is based on the document Recommended procedure for treating COVID-19.

The active substance *hydroxychloroquine* suppresses the overproduction of cytokine as part of the "cytokine storm" which causes the very serious course of the disease with damage to a number of vital organs. Furthermore, the active substance *hydroxychloroquine* raises the pH in endosomes, lysosomes and the Golgi apparatus, whereas endosomes are important in the process of virus penetration into cells. It also disrupts the glycosylation of angiotensin, which converts type 2 enzyme (ACE2), a membrane protein through which the virus binds itself to the target cells; hence it blocks the penetration of the virus into cells on two levels.

The medicinal product PLAQUENIL, which contains the active substance *hydroxychloroquine sulphate,* is registered and marketed in the Czech Republic. Based on the summary of product characteristics, this medicinal product is indicated for the treatment of adults suffering from systemic lupus erythematosus, discoid lupus erythematosus, rheumatoid arthritis and photodermatosis. In the paediatric population, the medicinal product PLAQUENIL is indicated for the treatment of juvenile idiopathic arthritis (in combination with other treatment), discoid and systemic lupus erythematosus. Other indications for the medicinal product PLAQUENIL are the prevention and treatment of acute attacks of malaria caused by *Plasmodium vivax*, *P. ovale and P. malariae* and sensitive strains of *P. falciparum*, and the radical treatment of malaria caused by sensitive strains of *P. falciparum*. Based on available information, the medicinal product PLAQUENIL is also applied in indications not listed in the summary of product characteristics (sarcoidosis, interstitial lung disease in children, Sjogren's syndrome with extraglandular manifestations, undifferentiated or mixed connective tissue diseases, overlapping syndromes between connective tissue diseases, dermatomyositis).

As it is desirable to ensure a sufficient quantity of medicinal products containing the active substance *hydroxychloroquine* both for patients with COVID-19 disease and for patients undergoing treatment for the aforementioned indications (i.e. the medicinal product PLAQUENIL), the Ministry of Health permits the distribution, dispensing and use of the non-

registered medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA. This medicinal product will be designated for treating patients in the Czech Republic with proven COVID-19 infection; treatment may be commenced exclusively within the framework of hospitalisation.

The dispensing of the medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA requires a doctor's prescription, as does the medicinal product PLAQUENIL, which contains the same active substance.

As the interior and exterior packaging of the medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA will be in the Dutch language, the distributor is obliged to include a summary of product characteristics in the Czech language when delivering the product to a pharmacy. The summary of product characteristics will also be published on the Institute's website (www.sukl.cz).

Given the fact that the medicinal product HYDROXYCHLOROQUINE-SULFAAT TEVA is not registered in the Czech Republic, one condition for its use when providing healthcare services is the informed consent of the patient (or their legal guardian).

The Ministry of Health has stipulated a date of effect for this decision of 8 months from the date of its posting on the official notice board. This period is stipulated based on the currently expected development of the COVID-19 epidemiological situation.

When handling this medicinal product, it is necessary to comply with the provisions of the Act on Pharmaceuticals, with the exception of the foregoing particularities.

Prof. MUDr. Roman Prymula, CSc., Ph.D.,
Deputy Minister of Health

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