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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Chloramphenicol VUAB 1 g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One injection vial contains chloramphenicol 1 g (as chloramphenicol sodium succinate 1.38 g).
One ml of reconstituted solution contains approximately chloramphenicol 67 mg.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Powder for concentrated solution for injection
White to yellowish-white freeze dried powder

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
Typhus and parathyphus, salmonellosis with septic development, meningitis, epiglottis, pertussis and parapertussis, serious infections with aerobe and anaerobe flora (pulmonary, abdominal, gynecologic) and other infections caused by bacteria susceptible to chloramphenicol.

Chloramphenicol VUAB 1 g can be used only in serious infections, for which less potentially dangerous drugs are ineffective or are contraindicated (see point 4.4. and 5.1.). Chloramphenicol is not indicated for neonates.

Official guidance for using of antibiotics must be taken in consideration.

4.2. Posology and method of administration
Posology
I.v. injection
The dosage depends on the severinity of infection. The recommended dosage:

Adults: the daily dose is 1 g (as chloramphenicol base), every 6 – 8 hours by parenteral application.

Elderly: The usual adult dosage should be given subject to normal hepatic and renal function.

Pediatric population
Children: The equivalent of 50 mg/kg chloramphenicol daily in divided doses every 6 hours (this dose should not be exceeded). The patient should be carefully observed for signs of toxicity.

Patients with impaired hepatic and renal function: Dosage must be sufficiently reduced. Continuous control of hepatic and renal function is performed concurrently.

In exceptional cases, such as patients with septicemia or meningitis, dosage schedule up to 100 mg/kg/day may be prescribed. However, these high doses should be decreased as soon as clinically indicated.

To prevent relapses treatment should be continued after the temperature has returned to normal for 4 days in rickettsial diseases and for 8 – 10 days in typhoid fever.

Substitution of i.v. chloramphenicol with suitable p.o. antibiotic must be done as soon as possible.

Method of administration
The solution is administered by i.v. infusion.

If i.v. application is not possible, the solution can be used i.m., but the absorption will be slow and unpredictable.

4.3. Contraindication
Hypersensitivity to the active substance.

4.4. Special warnings and precautions for use
Chloramphenicol is to be administered only under the direction of a physician.

Chloramphenicol is not suitable for sanitation of salmonella carriers.

Chloramphenicol should not be used in the treatment of any infection for which a less toxic antibiotic is available. Chloramphenicol must not be used as prophylaxis. Chloramphenicol must be reserved for cases, in which other, less toxic antibiotic cannot be used.

Chloramphenicol may cause severe bone marrow depression which may lead to agranulocytosis, thrombocytopenic purpura or aplastic anemia. These effects of the haemopoietic system are usually associated with a high dose, prolonged administration, or repeated courses, but they may occur at relatively low doses.

It is also advisable to perform blood tests in the case of prolonged or repeated administration. Evidence of any detrimental effect on blood elements is an indication to discontinue therapy immediately.

If it is possible, repeated administration of chloramphenicol must be avoided.

Because of its toxic nature it is important to monitor serum levels of this antibiotic particularly in new-born and premature infants, in the elderly, in patients with renal or hepatic disease and in those receiving other drugs with which chloramphenicol may interact.

Treatment with chloramphenicol can infest unsusceptible Clostridium difficile and caused severe diarrhea. Treatment with chloramphenicol can infest unsusceptible microorganisms including fungi.

Chloramphenicol for injection is not effective in local application. The active moiety is generated by hepatic enzymes. For local application non-esterificated chloramphenicol should be used. If local therapy is necessary; it should always be accompanied with systemic treatment with chloramphenicol.

4.5 Interaction with other medicinal products and other forms of interaction
Combination with bactericide antimicrobial drugs (penicillin's, cephalosporin's, macrolide antibiotics) can have antagonistic effect. Thus, this approach is not suitable for the treatment.

Aminophenason, carbimasol and other drugs associated with bone marrow depression should not be prescribed during the course of treatment with chloramphenicol.

By inhibition of microsomal enzymes chloramphenicol reduces biodegradation and prolongs effect of phenytoin, some of the oral antidiabetics (tolbutamide, chlorpropamide) and indirect anticoagulants (warfarine, dicumarol). During the concurrent treatment, dose adjustment may be necessary.

Phenobarbital and rifampicine could increase biodegradation of chloramphenicol due to hepatic enzymes induction.

Chloramphenicol increases plasma levels of tacrolimus, probably by inhibition of biodegradation of tacrolimus. In cases of concurrent administration, plasma levels of tacrolimus should be monitored and dosage should be adjusted as needed.

Paracetamol reduces detoxification and prolongs half-life of chloramphenicol.

Chloramphenicol reduces the effect of cyclophosphamide and increases the effect of methotrexate.
Chloramphenicol causes alcohol intolerance and reduces the effect of iron preparations, vitamin B_{12} and folic acid on haematopoiesis.

4.6. Fertility, pregnancy and lactation
Pregnancy:
Reproduction studies of chloramphenicol have not been performed on animals. There are no adequate controlled studies guaranteeing safety of chloramphenicol administered during pregnancy. It is not known whether chloramphenicol can cause fetal harm when it is used in pregnancy. Orally administered chloramphenicol crosses the placental barrier. Because of the potential toxic effect on the fetus (see section 4.8 gray syndrome), chloramphenicol may be administered to a pregnant woman only if the potential benefit outweighs the potential risk for fetus.

Lactation:
Orally administered chloramphenicol passes into breast milk. Chloramphenicol should not be administered to breastfeeding woman, especially if a woman breastfeeds a premature baby or neonate in the first weeks of life. Chloramphenicol can be administered to breastfeeding woman only rarely, if necessary, after evaluation of the benefits and the risks, when it is impossible to administer another antibiotic with favorable safety profile. In such cases, it is necessary to monitor the child because of the possible occurrence of side effects. In infants whose mothers have taken chloramphenicol oral 1 – 3 g per day, side effects such as abnormal milk sucking, falling asleep on the breast, vomiting after breastfeeding, excessive flatulence and abdominal distension, were observed. At the dose of 3 g/day these events were observed in most breastfed babies. The risk of idiosyncratic aplastic anemia should also be taken into consideration, although it has never been observed in breastfed babies.

4.7. Effects on ability to drive and use machines
Unknown, irrelevant.
Chloramphenicol VUAB 1 g is used in hospitalized patients.

4.8. Undesirable effects
Undesirable effects occur in approximately 10% of patients. There are no sufficient data available from clinical trials to demonstrate the rate of appearance.

Most serious undesirable effects:
Blood and lymphatic system disorders
- Reversible depression of bone marrow with reticulocytopenia, leukopenia, thrombocytopenia and hematocrit decrease; dose dependent, occurs during and after the treatment, and normalizes within 10 - 20 days after the discontinuation of the therapy.
- Irreversible progressive aplastic anemia. Dose independent occurs after 2 to 4 months after the discontinuation treatment with chloramphenicol, possibly even longer.

The main cause is probably based on immunological changes in the body especially following repeated (including local) treatment with chloramphenicol.
– Gray syndrome (gray cyanosis) in neonates, particularly in premature infants, in which competition of the oxygen and chloramphenicol in the hemoglobin molecule occurs. It is caused by an insufficient ability of the liver to conjugate chloramphenicol with glucuronic acid. Further immaturity of renal tubular epithelium applies as well.

Other undesirable effects (frequency is unknown):

Blood and lymphatic system disorders
Granulocytopenia, hypoplastic anemia, pancytopenia, thrombocytopenia, risk of haemolytic anemia in patients with glucose-6-phosphatedehydrogenase deficiency, paroxysmal nocturnal haemoglobinuria.

Nervous system disorders
Confusion, delirium, depression, headache, peripheral neuritis, optical and vestibulocochlear neuritis. (Vision impairment is usually reversible in early drug discontinuation, but irreversible vision impairment and blindness have been observed too.)

After fast i.v. infusion patients can have intensive bitter taste.

Gastrointestinal disorders
Nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis.

General disorders and administration site conditions
Fever.
Jarisch-Herxheimer (endotoxin) reaction may occur following the administration of higher dosed (e.g. in treatment of typhoid).

In patients suffering from dystrophies, bleeding disorders may occur following long term administration due to depression of the bacterial intestinal flora producing vitamin K.

Immune system disorders
Rash, angioedema, anaphylactic reaction.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9. Overdose
General supportive therapy is recommended.
There is a risk of overdose in patients with hepatic and renal disorders. Increased level of blood chloramphenicol causes symptoms of bone marrow suppression. Appearance of this type of haematopoeitic disorder is dose independent and it occurs 2-4 months after discontinuation of the chloramphenicol administration.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antibacterial drugs for systemic using, amphenicols
ATC code: J01BA01

Mechanism of action
Chloramphenicol is synthetic broad-spectrum antibiotic. Chloramphenicol is reserved only for severe infections caused by susceptible microorganisms, which can not be treated by other, less toxic antibiotic.

Chloramphenicol belong among amphenicols, is high lipophilic and penetrates by passive diffusion into cell. Chloramphenicol inhibits peptidyltransferase in prokaryotes. Peptidyltransferase is part of a large 50S subunit of ribosome and participates is biosynthesis of proteins. It is the enzyme that catalyses the formation of peptide bonds during translation.

Chloramphenicol is highly effective against Salmonella, Yersinia, Haemophilus, bordetellas, gonococci, meningococci and anaerobic microorganisms; brucella, francisellas, leptospiras and Treponemes, corynebacteria, listeria, bacillus anthrax, actinomycetes, mycoplasma and chlamydia, and Rickettsiae are also well sensitive. Furthermore, most (60-80% of the strains) of Gram-negative rods (Escherichia coli, Enterobacter, Klebsiella, Citrobacter, Proteus, Providencia, Shigella etc.), and enterococci are also sensitive.

Although streptococci and pneumococci are very sensitive to chloramphenicol, penicillin preparations are preferred. Staphylococci are also generally sensitive to chloramphenicol (about 70% of strains), but anti-staphylococcal antibiotics could usually achieve better therapeutic results. Indole-positive strains of Protea, Enterobacter spp., Citrobacter spp., Pseudomonas aeruginosa and mycobacteria are generally resistant.

The mechanism of resistance
There are 3 mechanisms participating in resistance to chloramphenicol:
– Mutation of the 50S ribosomal subunit
– change the permeability of membrane
– resistance depends on the presence of R factor encoding acetyl-CoA transferase inactivating chloramphenicol

Thresholds
EUCAST clinic MIC breakpoints

Relating to variety	(S≤/R>)
Enterobacteriaceae	8/8
Pseudomonas	N
Acinetobacter	N
Staphylococcus	8/8
Enterococcus	N
Streptococus A,B,C,G	8/8
S. pneumoniae	8/8
Other streptococci	N
H. influenzae, M. catarrhalis	1/2
N. gonorrhoeae	N
N. meningitis	2/4
Gram-positive anaerobes	8/8
Gram-negative anaerobes	8/8

N: Test of susceptibility is not recommended.

5.2. Pharmacokinetic properties
Following the parental administration, the ester of sodium-chloramphenicol-succinate is hydrolysed by tissue enzymes and free chloramphenicol levels approximately as high as the levels that would follow oral administration of identical dose are achieved. Chloramphenicol penetrates into cerebrospinal fluid and produces measurable concentrations, in bronchial secretions, lungs, pleural fluid, bile, peritoneum, ascitus, saliva, breast milk, ocular fluid and bones. In tissues, it reaches approximately 50 percent of serum concentration. Chloramphenicol is excreted in urine, only 5 – 15% of chloramphenicol is secreted in a biologically active form, the rest is secreted in the form of glucuronides. During 8 hours following the administration, 50 – 65% of the total amount administered is excreted in urine. Half-time is 2,5 – 5 hour, in case of anuria it is 7 hours, in case of hepatic insufficiency 5 – 13 hours. Chloramphenicol is not dialyzed during either haemodialysis or peritoneal dialysis. Active substance crosses placental barrier. The concentrations in umbilical blood are somewhat lower in comparison with maternal blood. Chloramphenicol passes into the breast milk (there is a risk of jaundice development in infants).

5.3. Preclinical safety data
Studies of carcinogen and mutagen potencial and influence on fertility were not performed.

6. PHARMACEUTICAL PARTICULARS
6.1. List of excipients
None.

6.2. Incompatibilities
Not Applicable

6.3. Shelf life
3 years
Product should be used immediately after opening of the vial

Chemical and physical in-use has been demonstrated for 24 hours when stored at 2 °C – 8 °C protected from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions after reconstitution are the responsibility of the user and would normally not be longer than 24 hours at 2 °C – 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Fractions which were not consumed within 24 hours, they must be disposed. The prepared solutions must not be steam-sterilized.

6.4. Special precautions for storage
This medicine does not require any special storage conditions. It is recommended to store at room temperature.

Store vial in the box in order to protect from light.

Storage conditions of the reconstituted medicinal product are listed in section 6.3.

6.5. Nature and contents of container
Glass vial, rubber stopper, aluminium cap or flip-off cap, box.

Package Size: 1 vial with 1 g

6.6. Special precautions for disposal
The powder should be reconstituted by addition of 15 ml of water for injection or solution of sodium chloride.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER
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8. REGISTRATION HOLDER:
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9. PRODUCT REGISTRATION NO.:
159-56-34926