health
Department:
Health
REPUBLIC OF SOUTH AFRICA

Private Bag X828, PRETORIA, 0001 Dr AB Xuma Building1112 Voortrekker Road, Pretoria Townlands 351-JR, PRETORIA, 0187 Tel (012) 395 8000, Fax (012) 395 8918

Mr E van Zyl
Equity Pharmaceuticals (Pty) Ltd
100 Sovereign Road
Route 21 Corporate Park
Nellmapius Drive
Irene
Pretoria

Dear Mr van Zyl

Section 21 Authorization for PHENOBARBITONE 30MG TABLETS 28'S

Attached, please find the Authorization for exemption under Section 21 of the Medicines and Related Substances Act by SAHPRA granted for:

- **Phenobarbitone 30mg Tablets 28's**

The quantities for which approval was granted are only estimates based on procurement by provinces over the last 6 months. Please note that the National Department of Health (NDOH) cannot guarantee the procurement of these quantities, as NDOH has no control over orders being placed by provincial depots, and current stock holding might influence estimated quantities.

The following process will be followed to ensure the quality of the product being brought in:

1. Manufacturer will submit an assay and identification of every batch imported.
2. An additional assay of every batch will be done by a quality control laboratory.
3. A random sample will be assayed during the authorized period by a quality control laboratory.
4. Aggregate statistics to be submitted to NDOH in the first week of each month of all orders received and quantities supplied per province.
5. The NDOH needs to be advised of the quantities and date of arrival of stocks in terms of this authorization within 7 days after arrival.
6. The supplier will provide monthly reports, by the 7th of each month, using the attached format of orders received and issues done.
7. Participating Authorities (PAs) will provide a consolidated close out report of usage using the attached format on the date when an authorization lapses.

8. The full quantities imported in terms of this Section 21authorisation must be accounted for.
9. Note that this authorization DOES NOT cover supplies to the private sector.
10. Where this authorization is obtained to provide security of supply due to supply challenges from the contracted supplier, PAs are requested to buy out against contracted suppliers and ensure that related orders are cancelled accordingly to prevent overstocking once the contracted supplier gets back into stock.

It should be noted this authorization applies only for use of the product in the public sector with estimated usage quantities for a period of one month. The authorization is expected to expire on **11 December 2026**.

Table 1: Provincial estimates

Province	Six Months Estimate
DCS	0
EC-MT	18 000
EC-PE	26 000
FS	7 200
GP	4 500
KZN	21 000
LP	25 000
MP	13 000
NC	11 000
NW	7 780
SAMHS	250
WC	19 000
Total	**152 730**

Yours sincerely

K Jamaloodien

KHADIJA JAMALOODIEN
CHIEF DIRECTOR: HEALTH PRODUCTS PROCUREMENT
DATE: 19/6/2026

S2100031225

SAHPRA
South African
Health Products
Regulatory Authority

SAHPRA Head Office
Building A, Loftus Park
2nd Floor
Kirkness Str
Arcadia
0083

Section 21 Outcome Letter

2026-06-18

Ms Khadija Jamaloodien

1112 Voortrekker Road

Pretoria

buhle.mbongo@health.gov.za

Dear Ms Khadija Jamaloodien

REQUEST TO USE UNREGISTERED MEDICINE IN TERMS OF SECTION 21 OF THE MEDICINES AND CONTROLLED SUBSTANCES ACT, 1965 (ACT 101 of 1965):

Your application dated **2026-06-11** refers

A. STATUS: Approved

B. APPLICANT: Ms Khadija Jamaloodien

C. IMPORTING COMPANY: EQUITY PHARMACEUTICAL (PTY) LTD

D. NUMBER OF PATIENT/(S) INTENDED TO BE TREATED: 10000

E. UNREGISTERED MEDICINES: GENERIC NAME: No Data

F. TRADE NAME: Phenobarbitone 30 mg

G. QUANTITY: 153215 Packs (28)

SAHPRA
South African
Health Products
Regulatory Authority

SAHPRA Head Office
Building A, Loftus Park
2nd Floor
Kirkness Str
Arcadia
0083

H. LETTER NUMBER: S2100031225

Section 21 authorization letters are valid for a period of 6 months from the letter date, unless otherwise specified.

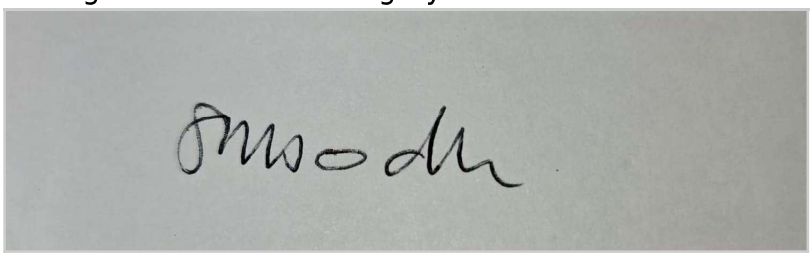
A progress report must be submitted once treatment is completed or on a reauthorization request

Comments:

Yours faithfully,

Dr Shyamli Munbodh

Manager: Section 21 Category A Medicines



Ms Mahlodi Moropa

Final Approver

S2100031225

SAHPRA
South African
Health Products
Regulatory Authority

SAHPRA Head Office
Building A, Loftus Park
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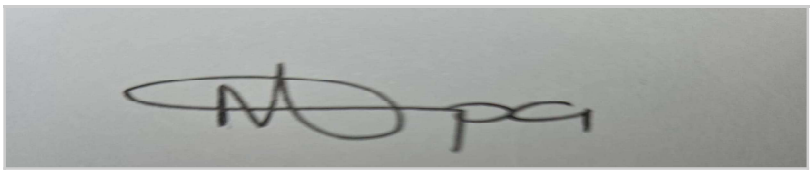

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REQUEST FOR QUOTATION FORM

- **Instruction to complete this Request for Quotation (RFQ)**
  PLEASE PROVIDE A QUOTE FOR THE FOLLOWING PRODUCT(S).
  PLEASE QUOTE ON THIS RFQ FORM AND ATTACH YOUR QUOTE WITH THE REQUESTED DETAILS.
  THE SECTIONS HIGHLIGHTED IN YELLOW MUST BE COMPLETED BY THE SUPPLIER.
- **THIS DOES NOT CONSTITUTE ANY OBLIGATION TO PROCURE THE ITEM AS THIS WILL BE SUBMITTED FOR CONSIDERATION TO PROVINCIAL PROCUREMENT UNITS TO SERVE AS A BUY OUT AGAINST CURRENT NON-COMPLIANT SUPPLIERS.**

ONLY RESPONSES FROM DULY REGISTERED SUPPLIERS WILL BE EVALUATED

REFERENCE NUMBER:	NORMAL		SECTION 21	X	S21RFQ176/2026
QUOTE ENQUIRY DATE	11/05/2026	QUOTE CLOSING DATE			22/05/2026
FOR CRITICAL DELIVERY, DELIVERY REQUESTED ON/BEFORE *(SCM Practitioner to Specify if applicable)*					

REQUESTING INSTITUTION CONTACT DETAILS

NAME OF REQUESTOR	Anzelde Willemse		
EMAIL ADDRESS	anzelde.willemse@health.gov.za		
PHONE No.	066 261 4234	FAX No.	N/A

PRODUCT INFORMATION

DESCRIPTION PER MPC	**Phenobarbital; 30mg; Tablet; 28 Tablets**		
TRADE DESCRIPTION	Phenobarbital 30mg tablets (1 x 28 tabs)		
UNIT OF MEASURE	Packs	PACK or BOX (*SIZE/ QUANTITY*)	28 Tablets
QUANTITY REQUIRED	**152 730**		

TO BE COMPLETED BY THE SUPPLIER/ SERVICE PROVIDER

SUPPLIER CONTACT DETAILS (as per CSD)

DID YOU BID ITEM FOR TENDER	YES		NO	X	IF NO, WHY	**Section 21**
COMPANY NAME	Equity Pharmaceuticals Pty Ltd					
SUPPLIER NUMBER	MAAA007480					
SECURITY CODE						
SUPPLIER CODE (NDoH)						

CONTACT PERSON 1	NAME	**Ehrard van Zyl**		
	PHONE	**012 345 1747**	FAX	**0123451412**
	MOBILE	*072 040 8511*		
	E-MAIL	**ehrard@equitypharma.co.za**		
CONTACT PERSON 2	NAME	**Hannes Strydom**		
	PHONE	**012 345 1747**		

	MOBILE	*082 616 1954*
	E-MAIL	**hannes@equitypharma.co.za**

QUOTE DETAILS			
PRICE PER UNIT (INCL. VAT)	R 25.07	TOTAL PRICE (INCL. DELIVERY & VAT)	R 3 828 941.10
VOLUMES AVAILABLE – 14DAYS			
VOLUMES AVAILABLE – 21DAYS			
VOLUMES AVAILABLE – 28DAYS			
VOLUMES AVAILABLE – 35DAYS			
VOLUMES AVAILABLE – 42DAYS			
VOLUMES AVAILABLE – 49DAYS			
VOLUMES AVAILABLE – 56DAYS	152 730 packs		
VOLUMES AVAILABLE – 112DAYS			
QUOTE VALIDITY PERIOD	180 days		
NORMAL LEAD/DELIVERY TIME	3 days		

DEVIATION TO SPECIFICATION
COMMENTS:

DECLARATION BY SUPPLIER
I hereby declare that in submitting this bid, there has been no consultation, communication, agreement or arrangement with any competitor/supplier regarding the price, quality, quantity, specifications and conditions or delivery particulars of the products or services to which this bid invitation relates.

NAME	**Ehrard van Zyl**
CAPACITY	**Business Unit Manager: Specialist Medicine**
SIGNATURE *(OF A DULY AUTHORISED REPRESENTATIVE OF THE SUPPLIER)*	
DATE	**22/05/2026**

PROVINCIAL ESTIMATES	
Province	**Six Months Estimate**
DCS	**0**
EC-MT	**18 000**
EC-PE	**26 000**
FS	**7 200**
GP	**4 500**
KZN	**21 000**
LP	**25 000**

MP	13 000
NC	11 000
NW	7 780
SAMHS	250
WC	19 000
Please submit quotations to anzelde.willemse@health.gov.za	

Please ensure that you include the following as part of the Quotation:

- Delivery Time (Weeks)
- Price (Vat Inclusive)
- Generic Name
- Trade Name
- Quotation on Official Company Letterhead
- Central Supplier Database Summary Report (CSD)
- Medicine Registration Certificate (Only for Locally Registered Products)
- *Artwork/Labelling
- *Package Insert: (Please attach)
- *Manufacturer Certificate: (Please attach)
- *Country of Origin: (Please indicate)

*Additional items required when submitting a quote for a Section 21 Item (Unregistered Medicine)
All of the above is required to expedite the process in considering the quotation.

Please ***SUBMIT COMPLETED RFQ FORM AND QUOTATIONS ON AN OFFICIAL COMPANY LETTERHEAD***

NB:

- The supplier submitting the quotation must be the same entity which the provinces will place their orders
- The size of each individual attachment must not be more than 2MB (you may attach multiple files in one email but collectively they should not be more than 2MB in size).
- Please ensure that you provide all prescribed documentation that is outlined on page two of this RFQ.
- The confirmation letter from manufacturer to Supply South Africa with Bivalent oral Poliomyelitis Vaccine (bOPV) must be provided (only in cases of Bivalent oral Poliomyelitis Vaccine RFQ)
- Kindly be advised that a picture format of an Artwork shall not be accepted. Artwork must be in pdf or word format only.
- All prices must please be submitted in two decimals and in ZAR.
- If submitting more than one quotation, please make sure that your subject line includes e.g., 1 of 2 or 1 of 3 etc.
- Any submission with missing documentation shall not be considered.
- Any submission with blurry relevant documents shall not be considered.
- The only electronic GMP Certificate considered is that from EUDRA
- CSD must be updated for the current month of the RFQ date.
- **Email subject line for responses with quotes must be kept unchanged from the originally sent RFQ email.**

Please ***SUBMIT COMPLETED RFQ FORM AND QUOTATIONS ON AN OFFICIAL COMPANY LETTERHEAD***

EQUITY
PHARMACEUTICALS

22/05/2026

Equity Pharmaceuticals (Pty) Ltd.
1997/009942/07

+27 12 345 1747
+27 12 345 1412
equity@equitypharma.co.za

www.clinigengroup.com
www.equitypharma.co.za

National Department of Health

Directorate: Affordable Medicines

E-mail: anzelde.willemse@health.gov.za

Attention: Ms Anzelde Willemse

Dear A Willemse

Re: Request for quotation – Phenobarbital 30mg tablets (28's) – Section 21 Supply

Trust you are well. Please find below our quotation for Phenobarbital 30mg Tablets (28's), supplied under section 21 terms.

• Quantity:	**152 730 packs**
• Delivery Time (Weeks):	**8 weeks**
• Price (Vat Inclusive):	**R 25.07 incl. vat per pack of 28's**
• Generic Name:	**Phenobarbital 30mg Tablets**
• Trade Name:	**Phenobarbital 30mg Tablets**
• Packaging:	**28's**
• Specifications:	**28 tablets per pack – Each tablet containing 30mg Phenobarbital B.P**
• Shelf Life:	**36 months**
• Package Insert:	**Please find attached**
• Manufacturer:	**Kwality Pharmaceuticals Ltd.**
• Country of Origin:	**India**

Please note that the immediate availability of the product is conditioned on the manufacturer receiving notice of our order as soon as possible. Unfortunately, the stock cannot be reserved for our purposes for too long.

We look forward to your response.

Please contact me if you require any additional information.

Kind Regards

Ehrard van Zyl

22/05/2026

Equity Pharmaceuticals (Pty) Ltd.
1997/009942/07

+27 12 345 1747
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equity@equitypharma.co.za

www.clinigengroup.com
www.equitypharma.co.za

QUOTATION # 20260522

TO: National Department of Health

TEL : 066 261 4234
FAX :
Email : anzelde.willemse@health.gov.za

CONTACT PERSON / PATIENT : Anzelde Willemse

NB IMPORTED AND SUPPLIED UNDER SECTION 21 TERMS

PRODUCT CODE	DESCRIPTION	PACK SIZE	QUANTITY	PRICE EXCL	TOTAL INCL
	Phenobarbital 30mg tablets (1 x 28 tabs)	28 tabs	1	R 21.80	R 25.07
			152 730	**R 3 329 514.00**	**R 3 828 941.10**
			152 730	**R 3 329 514.00**	**R 3 828 941.10**

Valid for 180 days

Employee Signature: _____

Date: 22/05/2026

Approved by: Ehrard van Zyl

100x170 mm front/back

Phenobarbital
Tablets BP 30 mg

COMPOSITION
Each tablet contains :
Phenobarbital BP ..... 30 mg.
Excipients ..... q.s.

CATEGORY
Barbiturate.

GENERAL INFORMATION
Phenobarbital & Amylobarbitone belong to the group Barbiturates of CNS depressants. They are hypnotic drugs.

MOA
Barbiturates are CNS depressants. They also augment inhibitory effects of GABA. Effects range from sedation and in high doses cause anaesthesia.

PHARMACOKINETIC
Phenobarbital has long plasma half life. Therefore, relatively constant serum level is maintained with single dose administration.
On Set of Action : Oral : 30-60 minutes.
Duration of Action : 24-48 hours. Some effect may persist upto 6 days.

INDICATIONS
Intractable insomnia, eclampsia, spastic excitatory states. Generalised tonic clonic seizures, febrile convulsion, temporal lobe epilepsy, cortical focal seizures, status epilepticus.

DOSAGE AND ADMINISTRATION
Adults: 30-210mg daily in divided doses.
Children: Phenobarbital:
1) For sedation : PO : 2-3 mg/kg/24hour divided every 8-12 hour.
2) For sleep: PO : 2-3 mg/kg/dose, repeat sos after 12-24 hour.
3) Long term anticonvulsant Rx: Start with 1.5mg/kg/24 hours, divided every 12 hours, increase according to tolerance and therapeutic effect to 4-6mg/kg/24 hour divided every 12 hours or as a single daily dose, preferably at bed time.

CONTRAINDICATIONS
Barbiturates are contraindicated in acute intermittent porphyria, uncontrolled pain and debilitated individuals and in cases of alcohol and drug abuse. Hyperkinetic children.

ADVERSE EFFECTS
Main side effect is sedation (which disappears after a few weeks due to development of tolerance). In young and elderly it causes confusion and paradoxical excitement or agitation. Irritability and hyperactivity in children may be seen. Megaloblastic anaemia, osteomalacia and skin rashes may occur. Rarely hepatitis and agranulocytosis may occur. The toxicity is manifested by hypotension, ataxia, dizziness, respiratory depression, coma & death.

SPECIAL PRECAUTIONS
Chronic use of barbiturates may result in intolerance and drug dependence. Barbiturates cause decreased efficacy of other drugs
because of hepatic microsomal enzyme induction in liver and accelerated metabolism of oral anticoagulants, oral contraceptives and phenytoin. Respiratory insufficiency.
Pregnancy : Use with caution.
Breast feeding : Use with caution.

Elderly : May be given in reduced dose.

INTERACTIONS
Alcohol & other CNS Depressants (other sedatives, hypnotics, anesthetics, antihistamines, tranquilizers, phenothiazines): Additive CNS depression.
Valproic acid: Increases efficacy of barbiturates. Half life of valproic acid may be decreased.
Chloramphenicol: Efficacy of barbiturates increased. Barbiturates may decrease efficacy of chloramphenicol.
MAOIs: Effects of barbiturates prolonged.
Efficacy of the following drugs decreased by barbiturates: Oral anticoagulants, digitoxin, TCAs, corticosteroids, doxycycline, oral contraceptives and estrogens, acetaminophen, beta-blockers, quinidine, rifampicin, theophylline and metronidazole.
Phenytoin: Effect on phenytoin metabolism is unpredictable.
Frusemide: May produce or aggravate orthostatic hypotension.
Griseofulvin: Interferes with absorption of oral griseofulvin leading to decreased blood levels.

STORAGE
Store between temperature 8° to 25°C. Protect from moisture.
Keep out of the reach of children.

PRESENTATION
Blister strip of 28 tablets are packed in a carton box.

Manufactured by:
Kwality Pharmaceuticals Ltd.
Nag Kalan, Majitha Road,
Amritsar -143601, INDIA


Phenobarbital
Tablets BP
30 mg
1 x 28 Tablets
30 mg
Phenobarbital
Tablets BP 30 mg
Batch No: 6122221
Mfg. Date 01/2024
Exp. Date 12/2027
Phenobarbital
Tablets BP 30 mg
1 x 28 Tablets

1 NAME OF THE MEDICINAL PRODUCT

Phenobarbital Tablets BP 30mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet containsPhenobarbital Ph Eur 30mg
Also contains Lactose Ph Eur 20.950mg
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

Smooth unmottled tablets showing no evidence of chipping or capping; free from specks and extraneous matter; odorless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Phenobarbital is recommended for all forms of epilepsy (except absence seizures).

4.2 Posology and method of administration

Posology
Adults: The usual dose is 60 – 180mg daily taken at night.

Children: 5- 8mg/kg body weight daily.

Elderly: Phenobarbital clearance diminishes in the elderly. Therefore, the dose of phenobarbital is usually lower in elderly patients.

The dose of phenobarbital should be adjusted to meet the needs to individual patients. This usually requires plasma concentration of 15 to 40 micrograms/ml (65 to 170 micromoles/litre).

Method of Administration
For oral administration.

4.3 Contraindications

Phenobarbital should not be given to patients with:

- Hypersensitivity to phenobarbital, other barbiturates or to any of the excipients listed in section 6.1.
- Acute intermittent porphyia
- Severe respiratory depression
- Severe renal or hepatic impairment

4.4 Special warnings and precautions for use

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Phenobarbital. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment. If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Phenobarbital treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed SJS or TEN with the use of Phenobarbital, Phenobarbital must not be re-started in this patient at any time.

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for Phenobarbital.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

<u>Women of childbearing potential</u>

Phenobarbital may cause foetal harm when administered to a pregnant woman. Prenatal exposure to phenobarbital may increase the risk for congenital malformations approximately 2- to 3-fold (see section 4.6).

Phenobarbital should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following consideration of other suitable treatment options. Women of childbearing potential should be fully informed of the potential risk to the foetus if they take phenobarbital during pregnancy.

A pregnancy test to rule out pregnancy should be considered prior to commencing treatment with phenobarbital in women of childbearing potential.

Women of childbearing potential should use highly effective contraception during treatment and for 2 months after the last dose. Due to enzyme induction, phenobarbital may result in a

failure of the therapeutic effect of oral contraceptive drugs containing oestrogen and/or progesterone. Women of childbearing potential should be advised to use other contraceptive methods (see sections 4.5 and 4.6).
Women planning a pregnancy should be advised to consult in advance with her physician so that adequate counselling can be provided and appropriate other treatment options can be discussed prior to conception and before contraception is discontinued.
Women of childbearing potential should be counselled to contact her doctor immediately if she becomes pregnant or thinks she may be pregnant while on treatment with phenobarbital.

Care should be used in the following situations:

- Respiratory depression (avoid if severe)
- Young, debilitated or senile patients
- Renal impairment
- Existing liver disease
- Sudden withdrawal should be avoided as severe withdrawal syndrome (rebound insomnia, anxiety, tremor, dizziness, nausea, fits and delirium) may be precipitated
- Acute chronic pain –paradoxical excitement may be induced or important symptoms masked.
- Prolonged use may result in dependence of the alcohol-barbiturate type. Care should be taken in treating patients with a history of drug abuse or alcoholism.

Important information regarding the ingredients in this medicine

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effects on Phenobarbital	Effects of phenobarbital on other medicines
• Alcohol –concurrent administration with alcohol may lead to an additive CNS depressant effect. This is likely with concurrent administration with other CNS depressants. • Antidepressants –including MAOIs, SSRIs and tricyclics may antagonise the antiepileptic activity of phenobarbital by lowering the convulsive threshold. • Antiepileptics - phenobarbital plasma concentrations increased by oxcarbazepine, phenytoin and sodium valproate.Vigabatrin possibly decreases phenobarbital plasma concentrations. • Antipsychotics –concurrent use of chlorpromazine and thioridazine with phenobarbital can reduce the serum levels of either drug. • Folic acid –if folic acid supplements are given to treat folate deficiency, which can	Phenobarbital increases the rate of metabolism reducing serum concentrations of the following drugs: • Anti-arrhythmics –disopyramide and quinidine loss of arrhythmia control is possible. Plasma levels of antiarrhymics should be monitored, if phenobarbital is added or withdrawn. Changes in dosage may be necessary. • Antibacterials –chloramphenicol, doxycycline, metronidazole and rifampicin. Avoid concomitant use of telithromycin during and for 2 weeks after Phenobarbital. • Anticoagulants. • Antidepressants –paroxetine, mianserin and tricyclic antidepressants. • Antiepileptics–carbamazepine, lamotrigine, tiagabine, zonisamide, primidone and possibly

be caused by the use of phenobarbital, the serum phenobarbital levels may fall, leading to decreased seizure control in some patients. (see section 4.6). • Memantine –the effect of Phenobarbital is possibly reduced. • Methylphenidate–plasma concentration of Phenobarbital is possibly increased. • St John's wort (Hypericum perforatum) – the effect of phenobarbital can be reduced by concomitant use of the herbal remedy St John's wort.	ethosuxamide. • Antifungals –the antifungal effects of griseofulvin can be reduced or even abolished by concurrent use. Phenobarbital possibly reduces plasma concentrations of itraconazole or posaconazole. Avoid concomitant use of voriconazole. • Antipsychotics –phenobarbital possibly reduces concentration of aripiprazole. • Antivirals –phenobarbital possibly reduces plasma levels of abacavir, amprenavir, darunavir, lopinavir, indinavir, nelfinavir, saquinavir. • Anxiolytics and Hypnotics –clonazepam. • Aprepitant –phenobarbital possibly reduces plasma concentration of aprepitant. • Beta-blockers –metoprolol, timolol and possibly propranolol. • Calcium channel blockers – phenobarbital causes reduced levels of felodipine, isradipine, diltiazem, verapamil, nimodipine and nifedipine and an increase in dosage may be required. • Cardiac Glycosides –blood levels of digitoxin can be halved by concurrent use. • Ciclosporin or tacrolimus. • Corticosteroids. • Cytotoxics –phenobarbital possibly reduces the plasma levels of etoposide or irinotecan. • Diuretics –concomitant use with eplerenone should be avoided. • Haloperidol- serum levels are approximately halved by concurrent used with phenobarbital. • Hormone Antagonists –gestrinone and possibly toremifene. • Methadone –levels can be reduced by concurrent use of phenobarbital and withdrawal symptoms have been reported in patients maintained on methadone when phenobarbital has been added. Increases in the methadone dosage may be necessary. • Montelukast. • Oestrogens –reduced contraceptive effect. • Progestogens –reduced contraceptive effect. • Sodium oxybate –enhanced effects, avoid concomitant use. • Theophylline –may require an increase in theophylline dose. • Thyroid hormones-may increase requirements for thyroid hormones in hypothyroidism. • Tibolone • Tropisetron • Vitamins –barbiturates possibly increase

	requirements for vitamin D

Patients treated concomitantly with valproate and phenobarbital should be monitored for signs of hyperammonemia. In half of the reported cases hyperammonaemia was asymptomatic and does not necessarily result in clinical encephalopathy.Phenobarbital may interfere with some laboratory tests including metyrapone test, phenlolamine tests and serum bilirubin estimation.

4.6 Fertility, pregnancy and Lactation

Women of childbearing potential/Contraception
Phenobarbital should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options.

A pregnancy test to rule out pregnancy should be considered prior to commencing treatment with phenobarbital in women of childbearing potential.

Women of childbearing potential should use highly effective contraception during treatment with phenobarbital and for 2 months after the last dose. Due to enzyme induction, phenobarbital may result in a failure of the therapeutic effect of oral contraceptive drugs containing oestrogen and/or progesterone. Women of childbearing potential should be advised to use other contraceptive methods while on treatment with phenobarbital, e.g. two complementary forms of contraception including a barrier method, oral contraceptive containing higher doses of estrogen, or a non-hormonal intrauterine device (see section 4.5).

Women of childbearing potential should be informed of and understand the risk of potential harm to the foetus associated with phenobarbital use during pregnancy and the importance of planning a pregnancy.

Women planning a pregnancy should be advised to consult in advance with her physician so that specialist medical advice can be provided and appropriate other treatment options can be discussed prior to conception and before contraception is discontinued.

Antiepileptic treatment should be reviewed regularly and especially when a woman is planning to become pregnant.

Women of childbearing potential should be counselled to contact her doctor immediately if she becomes pregnant or thinks she may be pregnant while on treatment with phenobarbital.

Pregnancy
Risk related to antiepileptic medicinal products in general
Medical advice regarding the potential risks to a fetus caused by both seizures and antiepileptic treatment should be given to all women of childbearing potential taking antiepileptic treatment, and especially to women planning pregnancy and women who are pregnant.

Antiepileptic treatment should be reviewed regularly and especially when a woman is planning to become pregnant. In pregnant women being treated for epilepsy, sudden discontinuation of antiepileptic drug (AED) therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.
As a general principle, monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs appear to be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AEDs.

Pregnancy
Risks related to phenobarbital
Phenobarbital readily crosses the placenta following oral administration and is distributed throughout fetal tissue, the highest concentrations being found in the placenta, fetal liver and brain.
Phenobarbital therapy in epileptic pregnant women presents a risk to the fetus in terms of major and minor congenital defects including congenital craniofacial and cardiac defects, digital abnormalities and, less commonly, cleft lip and palate. Studies in women with epilepsy who were exposed to phenobarbital during pregnancy identified a frequency of major malformations of 6-7% in their offspring compared to the background rate in the general population of 2-3%. Studies have found the risk of congenital malformations following in-utero exposure to phenobarbital to be dose-dependent, however, no dose has been found to be without risk. Therefore, the lowest effective dose should be used.

Adverse effects on neurobehavioral development have also been reported. Studies investigating neurodevelopmental effects of prenatally administered phenobarbital were mostly small in numbers; however, significant negative effects on neurodevelopment and IQ were found following in utero and postnatal exposure.
Animal studies (literature data) have shown
reproductive toxicity in rodents (see section 5.3).Data from meta-analysis and observational studies showed a risk of major
malformations about 2 to 3 times higher than the baseline risk of major malformations in the general population (which is 2-3%). The risk is dose-dependent; however, no dose has been found to be without risk. Phenobarbital monotherapy is associated with an increased risk of major congenital malformations, including cleft lip and palate and cardiovascular malformations. Other malformations involving various body systems including cases of hypospadias, facial dysmorphic features, neural tube effects, craniofacial dysmorphia (microcephaly) and digital abnormalities have also been reported.

Data from a registry study suggest an increase in the risk of infants born small for gestational age or with reduced body length to women with epilepsy who were exposed to phenobarbital during pregnancy compared to women exposed to lamotrigine monotherapy during pregnancy.

Neurodevelopmental disorders have been reported among children exposed to phenobarbital during pregnancy. Studies related to the risk of neurodevelopmental

disorders in children exposed to phenobarbital during pregnancy are contradictory and a risk cannot be excluded. Pre-clinical studies have also reported adverse neurodevelopment effects (see section 5.3).

Phenobarbital should not be used during pregnancy unless the potential benefit is judged to outweigh the risks following consideration of other suitable treatment options.

If, following re-evaluation of treatment with phenobarbital, no other treatment option is suitable, the lowest effective dose of phenobarbital should be used. The woman should be fully informed of and understand the risks related to the use of phenobarbital during pregnancy.

When used in the third trimester of pregnancy, withdrawal symptoms may occur in the neonate, including sedation, hypotonia and sucking disorder.

Patients taking phenobarbital should be adequately supplemented with folic acid before conception and during pregnancy (see section 4.5).
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Folic acid supplementation during pregnancy can help to reduce the risk of neural defects to the infant.

Haemorrhage at birth and addiction are also a risk. Prophylactic treatment with vitamin K1 for the mother before delivery (as well as the neonate) is recommended, the neonate should be monitored for signs of bleeding.

Breast-feeding
Phenobarbital is excreted into breast milk and there is a small risk of neonatal sedation. Breast feeding is therefore not advisable.

4.7. Effects on Ability to Drive and Use Machines

Phenobarbital may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Patients should be advised to make sure they are not affected before undertaking any potentially hazardous tasks.

4.8 Undesirable effects

- *Blood and the lymphatic system disorders:* megaloblastic anaemia (due to folate deficiency), agranulocytosis, thrombocytopenia.
- *Musculoskeletal and connective tissue disorders:* Dupuytren's contracture, frozen shoulder, arthralgia, osteomalacia, rickets.

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with phenobarbital. The mechanism by which phenobarbital affects bone metabolism has not been identified.

- *Reproductive and breast disorders:* Peyronie’s disease

- *Psychiatric disorders:* paradoxical reaction (unusual excitement), hallucinations, restlessness and confusion in the elderly, mental depression, memory and cognitive impairment, drowsiness, lethargy.
- *Nervous system disorders:* hyperactivity, behavioral disturbances in children, ataxia, nystagmus.
- *Cardiac disorders:* hypotension.
- *Respiratory disorders:* respiratory depression.
- *Hepato-bilary:* hepatitis, cholestasis.
- *Skin and subcutaneous tissue disorders:* allergic skin reactions (maculopapular morbilliform or scarlatiniform rashes), other skin reactions such as exfoliative dermatitis, erythema multiforme are rare. *Very Rare:* Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4).

- *General disorders and administration site conditions:* antiepileptichypersensitivity syndrome (features include fever, rash, lymphadenopathy, lymphocytosis, eosinophilia, haematological abnormalities, hepatic and otherorgan involvement including renal and pulmonary systems which may become life threatening).

4.9 Overdose

Toxicity varies between patients; tolerance will develop with chronic use. Features of poisoning are to be expected after ingestion of 1g in adults.

Features:

Drowsiness, dysarthria, ataxia, nystagmus and disinhibition. There may also be coma, cardiovascular collapse, cardiac arrest, hypotension, hypotonia, hyporeflexia, hypothermia, hypotension and respiratory depression. Barbiturates decrease gut motility, which may lead to slow onset and worsening of symptoms or cyclical improvement and worsening of symptoms.

Management:

Consider activated charcoal (50g for an adult, 10-15g for a child under 5 years) if more than 10mg/kg body weight of phenobarbital has been ingested within 1 hour, provided the airway can be protected. Repeat dose activated charcoal is the best method of enhancing elimination of phenobarbital in symptomatic patients. In severe hypotension dopamine or dobutamine can be used. Treat rhabdomyolysis with urinary alkalinistion. Haemodialysis or haemofiltration may be required for cases of acute renal or severe hyperkalaemia. Charcoal haemoperfusion is the treatment of choice for the majority of patients with severe barbiturate poisoning who fail to improve, or who deteriorate despite good supportive care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N03A A02,

Pharmacotherapeutic group: Antiepileptics.

Phenobarbital is a long-acting barbiturate, which because of its depressant effect on the motor cortex, is used in the treatment of epilepsy.

Phenobarbital has a widespread depressant action on cerebral function. It has sedative effects and has some protective action against all varieties of human partial and generalised epilepsy, with the exception of absence seizures. Phenobarbital is also effective in preventing seizures in the corresponding experimental animal models of epilepsy. In different studies Phenobarbital appears to have had inconsistent effects in suppressing experimental epileptic foci, and epileptic after-discharges, but it inhibits synaptic transmission, at least in the spinal cord. The drug's probable biochemical mechanism of action is through prolonging the opening time of Cl- ion channels in postsynaptic neuronal membranes. This effect causes membrane hyperpolarisation and thus impairs nerve impulse propagation. Phenobarbital also decreases intraneuronal Na+ concentrations, and inhibits Ca2+ influx into depolarized synaptosomes. It raises brain serotonin levels, and inhibits noradrenaline (norepinephrine) reuptake into synaptosomes. These additional biochemical actions may contribute towards the anticonvulsant effects of the drug.

5.2. Pharmacokinetic Properties

Absorption –phenobarbital is readily absorbed from the gastrointestinal tract, although it is relatively lipid –insoluble; peak concentrations are reached in about 2 hours after oral administration.

Distribution –phenobarbital is about 45 to 60% bound to plasma proteins. Phenobarbital crosses the placental barrier and is distributed into breast milk.

Metabolism –the plasma half life is about 75 to 120 hours in adults but is greatly prolonged in neonates, and shorter (about 21 to 75 hours) in children. There is considerable interindividual variation in phenobarbital kinetics. Phenobarbital in only partly metabolised in the liver.

Elimination –about 25% of a dose is excreted in the urine unchanged at normal urinary pH.

5.3. Preclinical Safety Data

Published studies reported teratogenic effects (morphological defects) in rodents exposed to phenobarbital. Cleft palate is reported consistently in all preclinical studies but other malformations are also reported (e.g. umbilical hernia, spina bifida, exencephaly, exomphalos plus fused ribs) in single studies or species.

In addition, although data from the published studies are inconsistent, phenobarbital given to rats/mice during gestation or early postnatal period was associated with adverse neurodevelopment effects, including alterations in locomotor activity, cognition and learning patterns.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch, pregelatinised

Lactose

Maize starch

Stearic acid

Water purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Blister strip packed in a carton

Pack sizes: 28 tablets

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

Kwality Pharmaceuticals Ltd

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Amritsar - 143601

India

MARKETING AUTHORISATION NUMBER(S)

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8

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9 17/11/2005

10 DATE OF REVISION OF THE TEXT

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