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List of Abbreviations

AUC	:	Area Under the plasma concentration-time Curve
AV-Block	:	Atrio-ventricular Block
BCS	:	Biopharmaceutical Classification System
C_{max}	:	Maximum (Peak) Concentration
CYP-P450	:	Cytochrome P450
EEG	:	Electroencephalogram
FSH	:	Follicle Stimulating Hormone
HF	:	Hot Flushes/flashes
i.v.	:	Intravenous
LH	:	Luteinizing Hormone
MAA	:	Marketing Authorisation Application
MHRA	:	Medicines and Healthcare products Regulatory Agency
$t_{1/2}$	:	Half-Life
T_{max}	:	Time to Maximum (Peak) Concentration
UK	:	United Kingdom

2.5 Clinical Overview

2.5.1 Product Development Rationale

In this marketing authorisation application (MAA), approval is sought by Syri Limited t/a Thame Laboratories for a marketing authorisation for Clonidine hydrochloride 50micrograms/5ml Sugar Free Oral Solution in accordance with Article 10(1) of Directive 2001/83/EC, as amended. Clonidine is indicated for the following conditions (SmPC-Dixarit, 2014):

- The prophylactic management of migraine or recurrent vascular headache.
- The management of vasomotor conditions commonly associated with menopause and characterised by flushing.

Migraine is classified as either episodic or chronic. The three main types of migraine (migraine without aura, migraine with aura and migraine aura without headache) account for the vast majority of migrainous headaches encountered in clinical practice. The epidemiological numbers of migraine may be misleading, as many patients who experience migraine do not consult their physicians. In many of the affected patients there is a family history of migraine. The first migraine attack is generally in childhood and over 80% patients have had their first attack by the age of 30. About 6% of men and 18% of women are affected by migraine; however among children, it is more common in boys compared to girls. The severity usually decreases with advancing years (EMIS Migraine 2014).

Hot flushes are thought to be related to changes in central nervous system neurotransmitters and peripheral vascular reactivity. The aetiology of hot flushes in menopause would seem to be related to low oestrogen levels as the ovaries fail, and the effect on central thermoregulation. During the menopausal transition, the frequency and severity of hot flushes and night sweats substantially increase. These symptoms are experienced by 70-80% of menopausal women and are most common in the first year subsequent to the last menstruation. Usually hot flushes last for 2-5 years, though some women may have symptoms for much longer (EMIS Hot Flushes 2015).

Clonidine was first discovered accidently in 1962 (Houston MC 1981 and Schmitt H 1977). In 1986, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a

marketing authorization to Boehringer Ingelheim Limited for clonidine (Dixarit Tablets 25 micrograms). Clonidine has therefore been authorised for more than 30 years in the UK, hence the period of data exclusivity has expired. The indications and dosage administration for the proposed drug product are the same as that of the reference product, (Dixarit Tablets 25 micrograms) marketed by Boehringer Ingelheim Limited. The proposed application is in accordance with Article 10(1) of the European Directive 2001/83/EC as amended, a generic application, hence no new clinical studies have been performed by the applicant. As clonidine has been in clinical use for more than 30 years, additional studies will not add any new information to the knowledge gained through its wide spread clinical use. This clinical overview contains a sufficient discussion of the published literature concerning the clinical pharmacology, efficacy and safety of clonidine drug product.

At present, clonidine is available within the European Union in the form of tablets and solution for injection. Since the proposed Clonidine hydrochloride 50micrograms/5ml Sugar Free Oral Solution is a generic product, it will offer an additional cost advantage over the existing branded products. An oral solution is developed to ease administration of the drug to patient populations who cannot easily swallow tablets.

2.5.2 Overview of Biopharmaceutics

In accordance with the CHMP guideline, "Note for Guidance on the Investigation of Bioavailability and Bioequivalence" (CPMP/EWP/QWP/1401/98Rev. 1/ Corr **), a BCS based bio-waiver is proposed.

Clonidine is a BCS class I drug exhibiting high solubility and high permeability (Varma MV et al 2005), and therefore is subject to the possibilities of a biowaiver. The BCS based bio-waiver is justified as below:

A) Solubility:

The pH-solubility profile of Clonidine hydrochloride in different pH media are given below as per in-house testing:

[redacted]

Based on above data, Clonidine hydrochloride at a 150µg dose (maximum daily dose) is readily soluble in a volume of 250ml which indicates that the drug is highly soluble.

B) Permeability:

Monolayer efflux study was carried out using multidrug resistance transfected MDCK type II (MDRI-MDCKII) cell lines. The values for clonidine are summarised in the table below (Varma MV et al 2005):

Table 2: Permeability data of clonidine

Compound	**$P_{app,AB}$ (nm/s)**	**$P_{app,BA}$ (nm/s)**	**Efflux ratio**	**% human intestinal absorption**
Clonidine	529.0	522.0	1.0	100

The permeability criterion from monolayer transport was set as $P_{app,AB} \leq 20$ nm/s for low permeability and $P_{app,AB} \geq 100$ nm/s for high permeability. Therefore, above data shows that clonidine having high permeability.

The permeability coefficients of Clonidine using *In vitro* could be used to predict the peroral absorption in both rat and human. In a study the permeability of clonidine in rats has been evaluated. The results obtained in the study and from literature are summarised below (Dowty ME et al 1997):

[redacted]

In another study, the gastrointestinal absorption of heterocyclic drugs was investigated with the Caco-2 cell model. The Caco-2 permeability and transport ratio of clonidine are summarised in the table below (Faassen F et al 2003):

Table 4: The Caco-2 permeability and transport ratio

Compound	**High conc.**			**Low conc.**		
	P_{app}, ab	**SD**	**P ratio**	**P_{app}, ab**	**SD**	**P ratio**
Clonidine HCl	2.18E-05	0.18	2.99	3.40E-05	0.00	2.95

Papp > $20x10^{-6}$ cm/s = high permeability

The permeability of clonidine in both the Caco-2/TC7 and HT29-MTX models was determined, and the ability of each model to predict intestinal absorption in humans was compared. The results are summarised in the table below (Pontier C et al 2001):

Table 5: Physicochemical Characteristics, Fraction Absorbed in Humans, and Transport Data using Caco-2 and HT29-MTX Models for Clonidine

Compound	Log Pa	Diffusion coeeficient ($x10^{-10}$ cm^2/S)		Papp ($x10^{-6}$ cm^2/S)		Absorbed fraction in human (%)
		Caco-2	HT29-MTX	Caco-2	HT29-MTX	
Clonidine	1.6	12.6	9.3	15.60±0.43	13.40±0.41	95

The solubility and permeability data above also confirm that Clonidine hydrochloride is BCS class I (high solubility and high permeability).

C) Comparative *in-vitro* dissolution study:

The applicant has conducted a comparative *in vitro* dissolution study between Clonidine hydrochloride 50mcg/5ml Oral Solution from Thame Laboratories and the reference product Dixarit 25mcg tablet of Boehringer Ingelheim Limited.

The study was conducted on pH 1.2, 4.5 and 6.8 using 5 time points (10, 15, 20, 30 and 45 minutes) for 12 sample units, and the results were compared.

The details of each dissolution study are given in the table below:

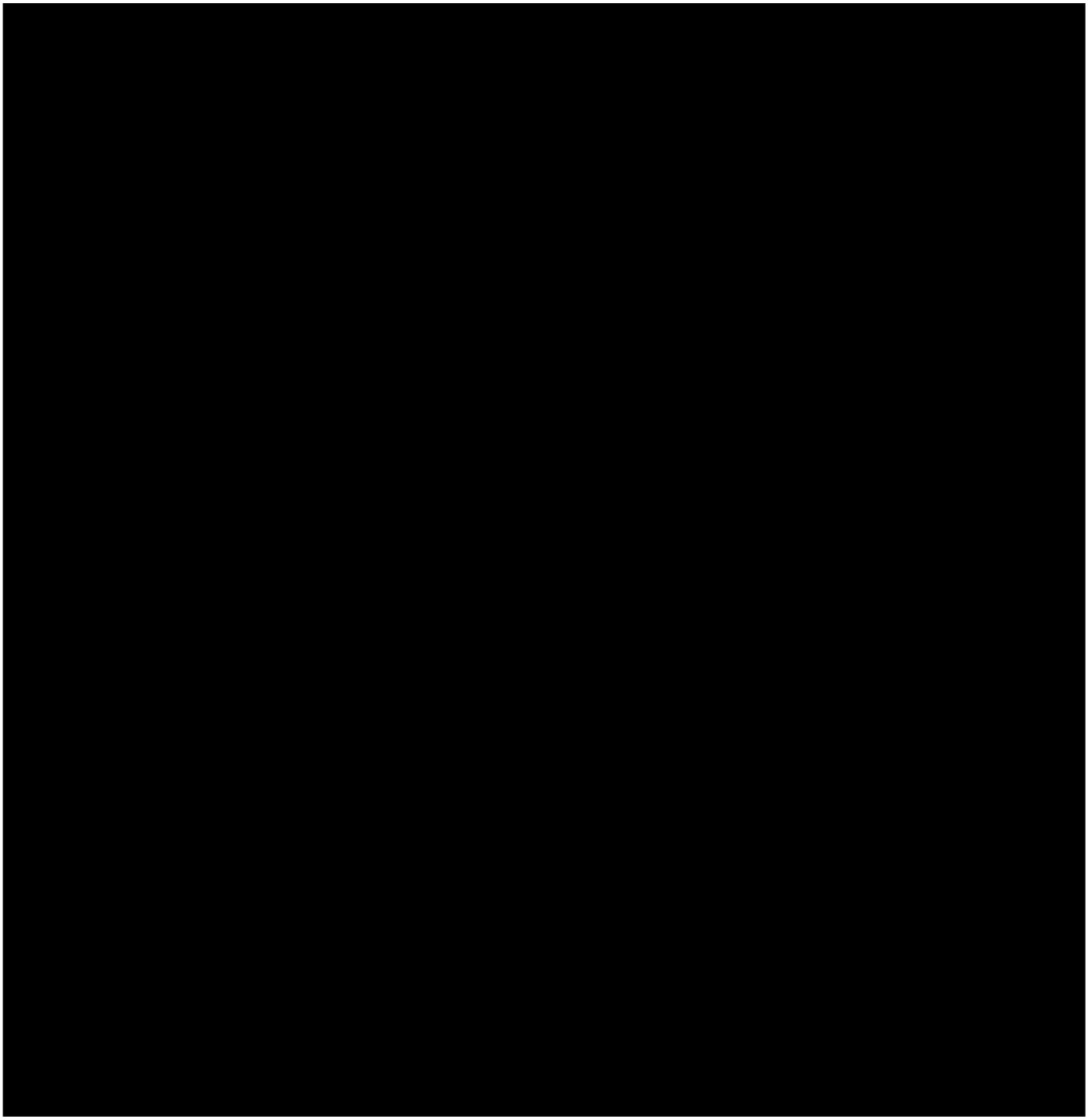
Table 6: Dissolution Parameters:

Sr. No.	Dissolution Media	Media volume	Label Claim	Sample dose	Apparatus	RPM	Time points
1.	0.1 N HCl pH 1.2	500ml	25 mcg tablet 50mcg/5ml	2 tablets 5ml	Paddle	75	10, 15, 20, 30 and 45 minutes
2.	Acetate buffer pH 4.5	500ml	25 mcg tablet 50mcg/5ml	2 tablets 5ml	Paddle	75	10, 15, 20, 30 and 45 minutes
3	Phosphate buffer pH 6.8	500ml	25 mcg tablet 50mcg/5ml	2 tablets 5ml	Paddle	75	10, 15, 20, 30 and 45 minutes

The results obtained at the three pH ranges are presented in the table below:

Table 7: Results from Comparative Dissolution

Sr. No.	Product Detail	Batch No.	Exp. Date
1.	Dixarit 25mcg tablet, Boehringer Ingelheim Limited **(Reference Product R)**	418508	March 2019
2.	Clonidine hydrochloride 50mcg/5ml Oral Solution Thame Laboratories **(Test Product T)**	CND-03-A-27	NA



D) Excipients:

Since the test product is a liquid and reference product is a solid dosage form, the excipients are not similar; however the test product does not contains any excipients at the level which might affect bioavailability.

Conclusion:

Based on the above data and discussion, the applicant requests the agency to grant a BCS based bio-waiver for Clonidine hydrochloride 50mcg/5ml Oral Solution.

Formulation

The excipients in Clonidine hydrochloride 50micrograms/5ml Sugar Free Oral Solution are methyl parahydroxybenzoate, sodium dihydrogen phosphate monohydrate, disodium phosphate anhydrous, sucralose and purified water. The excipients used in the proposed Clonidine hydrochloride 50micrograms/5ml Sugar Free Oral Solution are strictly controlled to the monograph requirements given in the current Ph. Eur. edition (European Pharmacopoeia) or BP (British Pharmacopoeia). These excipients are widely used in pharmaceutical products and are well-established.

Impurities Profile

The specification of the drug product contains limits for single maximum unknown impurity and total impurities. The specification limits for these impurities are shown in the table below:

These limits have been incorporated and monitored in the stability data.

2.5.3 Overview of Clinical Pharmacology

Mechanism of Action

Clonidine is an α-adrenergic agent that appears to act on bo th peripheral and central structures. Clonidine acts centrally to produce its antihypertensive effects by stimulating α_2-adrenergic receptors. Activation of these central alpha-adrenergic receptors diminishes the sympathetic tone to the heart, kidneys, and peripheral vasculature causing vasodilatation and lowering blood pressure. Peripherally clonidine is a typical alpha-sympathomimetic agent. Treatment with clonidine diminishes the responsiveness of peripheral vessels to constrictor and dilator stimuli, thereby preventing the vascular changes associated with migraine. The same direct action on peripheral vessels moderates the vascular changes associated with menopausal flushing (SmPC-Dixarit, 2014, Schmitt H 1977, Jarrott B et al 1987, Houston MC 1981, Onesti G et al 1971 and Toxnet 2012).

Numerous clinical studies have demonstrated the mechanism of clonidine at the α-adrenergic receptors and for the treatment and prophylaxis of migraine and flushing. These studies have been summarized below.

Pharmacodynamics

Clonidine, an alpha-adrenergic agonist used clinically for the treatment and prophylaxis of migraine, has been found to exert a beneficial effect on menopausal flushing, in particular by decreasing the intensity of the flushes. The menopausal hot flush is associated with a rapid increase in peripheral blood flow. Stressful mental arithmetic, which also increases peripheral blood flow, may evoke a hot flush. It seems possible that the alleviating effect of clonidine on the sensations of the flush could be mediated through an influence on vascular activity.

Ginsburg and colleagues have reported the effects of clonidine on cardiovascular responses to noradrenaline, adrenaline and angiotensin. The authors of this study found a dramatic effect of systemic clonidine on adrenergic responses in skeletal muscle vessels. The dilator effects of angiotensin in the forearm were abolished after clonidine which suggests that the drug may also alter vascular smooth muscle responsiveness independently of any influence on adrenergic mechanisms. Conclusively, the authors suggested a possible influence of the drug on vascular responsiveness not necessarily limited to an effect on adrenergic mechanisms and

which has therapeutic implications for both migraine and menopausal flushing (Ginsburg J et al 1985 and Ginsburg J et al 1987).

Postmenopausal women with hot flashes have significantly higher levels of central sympathetic activation compared with asymptomatic women. This produces elevated brain norepinephrine levels which reduce the sweating threshold in symptomatic women, thereby contributing to the initiation of menopausal hot flashes. The pharmacodynamic effects of clonidine involve the reduction of central sympathetic activation and thus lead to the amelioration of hot flashes.

The following study determined the effects of clonidine on the sweating threshold in symptomatic and asymptomatic postmenopausal women. Participants (12 healthy postmenopausal women reporting frequent hot flashes and 7 reporting none) received an intravenous injection of clonidine HCl (2 mg/kg of body weight), followed by body heating. The main outcome measures included core body temperature.

Core body temperature in homeotherms is regulated between upper thresholds for sweating and vasodilation, and lower thresholds for shivering. Clonidine significantly increased this threshold in symptomatic women but lowered it in asymptomatic women. These findings demonstrate the pharmacodynamic effects of clonidine involved in reducing hot flushes in postmenopausal women (Freedman RR et al 2000).

The pharmacodynamic properties of clonidine are reported to be dose-proportional (Frisk-Holmberg M et al 1978, Hogan MJ et al 1981 and Wing LM et al 1977) and remain stable during multiple dosing (Arndts D et al 1983). Studies have suggested a therapeutic window of 0.8 to 2.0 ng/ml within which clonidine exerts its hypotensive effects. A plasma concentration of clonidine greater than 2 ng/ml is associated with decreased antihypertensive effects due to peripheral alpha-adrenoceptor stimulation (SmPC-Dixarit, 2014 and Lowenthal DT et al 1983).

Pharmacokinetics

The pharmacokinetics of clonidine is dose-proportional in the range of 75-300 micrograms; over this range, dose linearity has not been fully demonstrated (SmPC-Dixarit, 2014; Arndts D 1983, Arndts D et al 1983 and Frisk-Holmberg M et al 1981).

The pharmacokinetic properties of clonidine remain stable during multiple dosing. The area under the curve (AUC), time to maximum concentration (t_{max}) and half-life ($t_{1/2}$) of clonidine did not change significantly between acute and chronic dosing studies (Arndts D 1983, Arndts D et al 1983 and Anavekar SN et al 1989).

The single oral dose kinetics of clonidine are similar to the i.v. kinetics at a comparable dose (Frisk-Holmberg M et al 1981, Arndts D et al 1983 and Lowenthal DT et al 1988).

The interpatient variability of the pharmacokinetics of clonidine is low (Anavekar SN et al 1982).

Absorption

Clonidine is highly absorbed. Absorption was rapid following administration of an oral dose, after an initial lag time of 19-22 minutes. The absorption half-life ranges between 18–22 minutes. Clonidine reaches peak plasma concentrations within 1-3h after oral administration (SmPC-Dixarit, 2014; Arndts D 1983, Anavekar SN et al 1982 and Arndts D et al 1983).

Clonidine shows 75 - 100 % bioavailability following administration of tablets or a sustained release formulation. This remains unaffected by m ultiple dosing (Arndts D 1983, Arndts D et al 1983 and Larsson P et al 2011).

The half-life ($t_{1/2}$), area under the curve (AUC), peak concentration (C_{max}) and time to reach peak concentration (T_{max}) for clonidine in 10 patients (4M / 6F, aged 20-42 years) were found to be similar for both the sublingual and oral routes (Cunningham FE et al 1994).

The steady-state plasma levels of clonidine (considering the minima only) are reached during day 4 (Arndts D 1983 and Arndts D et al 1983).

Distribution

Clonidine is rapidly and extensively distributed into tissues and crosses the blood-brain barrier, as well as the placental barrier (SmPC-Dixarit, 2014, Glynn CJ et al 1992, Boutroy MJ et al 1988 and Buchanan ML et al 2009).

The plasma protein binding of clonidine is 30-40 %. Studies using human albumin have demonstrated that the plasma protein binding of clonidine is independent of the concentration of clonidine in the solution. The beta (β) and gamma (γ) globulins are not involved in its plasma protein binding (SmPC-Dixarit, 2014 and Lowenthal DT et al 1980).

There is a large volume of distribution of 3.19-5.56L/kg after oral administration of clonidine (Lowenthal DT et al 1980). There is no evidence of drug accumulation of clonidine (Boswell G et al 1997 and Beckett AH et al 1989).

Clonidine is found in human milk; however, there is insufficient information on the effect on newborns (SmPC-Dixarit, 2014).

Metabolism

Clonidine undergoes a minor first pass effect (SmPC-Dixarit, 2014). There are five CYP-P450 enzymes (CYP2D6, 1A2, 3A4, 1A1, and 3A5) in human liver microsomes that are jointly responsible for 4-hydroxylation of clonidine to catalyze formation of 4-hydroxyclonidine. Selective inhibition studies confirmed that CYP2D6 accounted for approximately two-thirds of the catalytic activity (Claessens AJ et al 2010).

At least 4 metabolites of clonidine have been detected in human urine (Keränen A et al 1978 and Darda S et al 1978). The main metabolite p-hydroxy-clonidine is pharmacologically inactive (SmPC-Dixarit, 2014). The metabolic pattern of clonidine is shown in the figure below (Schmitt H 1977):

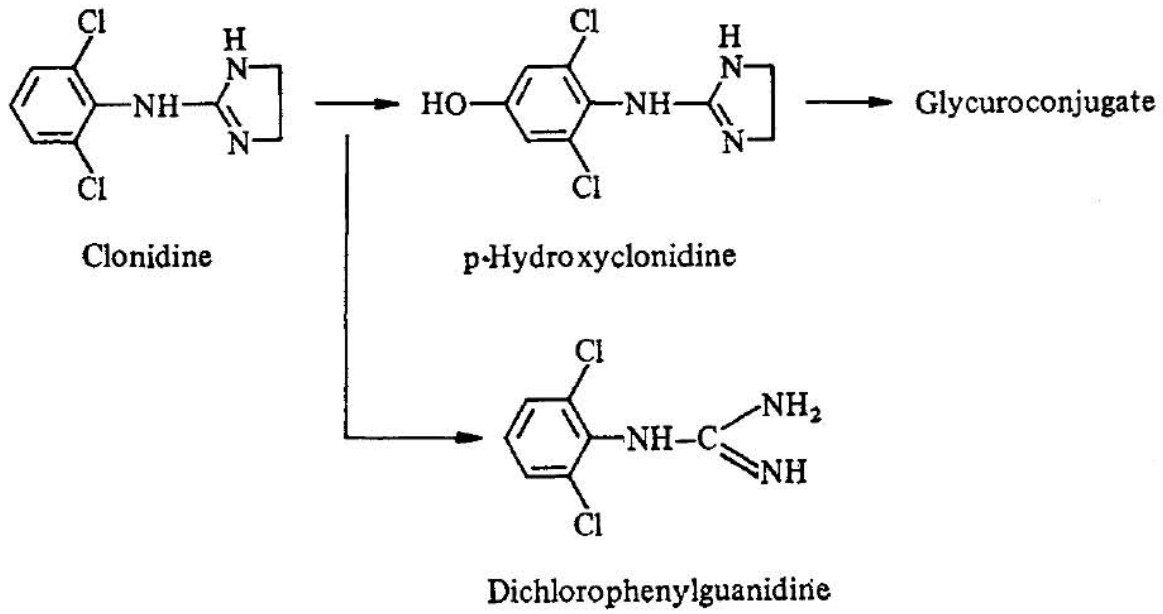


Figure 1: The metabolic pattern of clonidine (Schmitt H 1977)

There does not appear to be any induced change in the metabolism of clonidine after continuous oral dosing for one week when compared to that of a single oral dose (Keränen A et al 1978).

Excretion

The plasma clearance of clonidine after single oral dose was 3.24-4.17 ml/min/kg which increased to 7.18 ml/min/kg after multiple oral doses (Frisk-Holmberg M et al 1981 and Anavekar SN et al 1982).

The urinary excretion of clonidine completes in 3-5 days (Keränen A et al 1978). Of the dose administered, about 70 % is excreted in the urine, mainly in form of the unchanged parent drug (40-60 % of the dose). This is independent of the administered dose, the formulation and the mode of administration (SmPC-Dixarit, 2014, Arndts D 1983, Arndts D et al 1983 and Keränen A et al 1978). Approximately 20% of the total amount is excreted in the faeces, out of which about 15% is unchanged drug (SmPC-Dixarit, 2014 and Keränen A et al 1978).

The terminal elimination half-life of clonidine has been found to range from 5 to 25.5 hours, irrespective of the drug formulations and their route of administration (SmPC-Dixarit, 2014; Arndts D 1983, Arndts D et al 1983 and Anavekar SN et al 1982).

Factors affecting Pharmacokinetics

Food

There is no definitive data about food effects on the pharmacokinetics of clonidine (SmPC-Dixarit, 2014).

Gender

Clonidine administration to hypertensive patients showed similar drug concentrations in men and women (Schwartz JB 2003).

Ethnicity

There is no definitive data about race effects on the pharmacokinetics of clonidine (SmPC-Dixarit, 2014).

Pharmacokinetics in Special Populations

Elderly Patients (aged 65 years or above)

No specific information on the use of this drug product in the elderly is available (SmPC-Dixarit, 2014). However, in a review by Lowenthal DT et al 1988, the possibility of change in the mean plasma concentrations of clonidine in elderly patients was discussed after transdermal administration. The values obtained in elderly patients (60-74 years) were found to be consistently lower than that reported in younger volunteers (18-45 years). Such changes were not investigated after oral administration.

Paediatric Patients

The oral bioavailability of clonidine in children (3-10 years) is found to be 55.4%, which is less than that reported in adults (70-100%) (Larsson P et al 2011). The clearance of clonidine in neonates is approximately one-third of that in adults and increases rapidly along with their postnatal age during the first month of life (Potts AL et al 2007 and Xie HG et al 2011).

Renal impairment

The terminal elimination half-life of clonidine may be prolonged to up to 41 hours in patients with severely impaired renal function. Patients with abnormal renal function are likely to accumulate the drug, causing elevated concentrations to levels greater than the therapeutic level (2ng/ml) (SmPC-Dixarit, 2014; Davies DS et al 1977, Lowenthal DT et al 1983 and Lowenthal DT et al 1988).

Hepatic impairment

Approximately 40% of an administered dose of clonidine undergoes oxidative metabolism in the liver leading to inactive metabolites; therefore, hepatic impairment is likely to change the pharmacokinetics of clonidine (Arenas-López S et al 2004).

Drug Interactions

Pharmacodynamic Drug Interactions

Concurrent administration of antihypertensive agents, vasodilators or diuretics, may lead to an increased hypotensive effect (SmPC-Dixarit, 2014 and Toxnet 2012).

Substances with alpha$_2$-receptor blocking properties, such as mirtazapine, may abolish the alpha$_2$-receptor mediated effects of clonidine in a dose-dependent manner (SmPC-Dixarit, 2014 and Abo-Zena RA et al 2000).

The concomitant use of beta-blockers and/or cardiac glycosides can cause bradycardia or dysrhythmia (atrioventricular (AV) block) in isolated cases. It cannot be ruled out that concomitant administration of a beta-receptor blocker will cause or potentiate peripheral vascular disorders. If during combined treatment with a beta-blocker there is need to interrupt or discontinue antihypertensive therapy, the beta-blocker must always be discontinued slowly first, (reducing the dose gradually to avoid sympathetic hyperactivity) and then clonidine, which should also be reduced gradually over several days if previously given in high doses (SmPC-Dixarit, 2014 and Anderson JR et al 2001).

Orthostatic hypotension may be provoked or aggravated by concomitant administration of tricyclic antidepressants or neuroleptics with alpha-receptor blocking properties. As the effects of clonidine can be antagonised by tricyclic anti-depressants, it may be necessary to

adjust the dosage of clonidine, if these agents are administered concurrently (SmPC-Dixarit, 2014 and Houston MC 1981).

Although there is no experience from clinical trials, the effect of tranquillisers, hypnotics or alcohol could theoretically be potentiated by clonidine (SmPC-Dixarit, 2014 and Houston MC 1981).

Serious adverse events including sudden death have been reported in concomitant use with methylphenidate. The safety of using methylphenidate in combination with clonidine has not been systematically evaluated (SmPC-Dixarit, 2014). However, a 16-week multicenter trial in children reported no significant interactions between clonidine and methylphenidate regarding cardiovascular outcomes (Daviss WB et al 2008 and Palumbo DR et al 2008).

Pharmacokinetic Drug Interactions

Clonidine has been reported to affect gastrointestinal motility and intestinal absorption; therefore, clonidine may alter the absorption pharmacokinetics of other drugs (Schiller LR et al 1984).

Renal processes that are regulated by the alpha-adrenergic system can be affected by clonidine due to its CNS action of diminishing peripheral alpha-adrenergic activity. This may affect the elimination pharmacokinetics of other drugs (Itskovitz HD 1980).

Rifampin, a known inducer of microsomal enzymes, does not alter the elimination kinetics of clonidine (Affrime MB et al 1981).

2.5.4 Overview of Efficacy

Efficacy in prophylaxis of migraine or recurrent vascular headache:

Study 1:

The following randomised, double-blind, cross-over trial reports the findings of Shafar and colleagues who compared the efficacy of clonidine with placebo for the prophylaxis of migraine. Patients were administered two tablets twice daily of clonidine (two tablets of 25µg (50µg) twice a day) or placebo tablets. Patients were asked to record on a diary card all migrainous symptoms (graded as mild, moderate, or severe). The number and severity of episodes of migraine were determined in 42 p atients (8M / 34F aged 18-66 years) by calculating a weighted score for the pre-treatment period, clonidine and placebo periods. The attack-rates on active and placebo medication are in each case derived from data relating to mean periods of treatment of 3.7 months, while the pretreatment period was a single month. The results are recorded in the table below.

Table 10: Mean numbers of attacks per month (n=42)

Attack	**Attack frequency (mean attacks/month) in:**		
	Pre-treatment period	**Clonidine period**	**Placebo period**
Severe	2.07	1.49	2.00
Moderate	2.57	2.11	2.28
Mild	3.71	2.62	2.67
Total	8.36	6.23	6.95
Weighted score	15.07	11.32	13.23

A comparison of the total attack rates showed significantly lower rates during both active and placebo treatment periods, relative to pre-treatment, with a trend toward greater reduction on active medication. Analysis of weighted scores showed that both clonidine and placebo were associated with improvement, with the mean weighted score during clonidine administration being lower ($P<0.1$) than that relating to placebo. In addition, the results above show that the advantage of active treatment with clonidine derives principally from a reduction in the numbers of severe attacks (Shafar J et al 1972).

Study 2:

Adam EI et al 1978 conducted a double blind study of clonidine in the treatment of migraine in a general practice. The drug was given prophylactically and patients were assigned by simple randomization to one of two treatment groups: Group one: Patients (n=38, 8M / 30F, mean age of 40 years) treated with clonidine during the first six months of the study and placebo control during the second six months. Group two: Patients (n=32, 3M / 29F, mean age of 35 years) treated with placebo control during the first six months of the study and clonidine during the second six months. The initial dosage for each treatment was one tablet (0.025 mg) three times a day, but this could be increased at subsequent visits to a maximum of two tablets three times a day (0.15 mg). Each patient kept a diary to record the time of onset and duration of each headache. During the trial, the frequency of headaches fell by about 60%. Severity of headaches were less with clonidine ($P<0.01$). There was also some evidence that headaches lasting more than 12 hours were less common during treatment with the drug. Conclusively, the authors suggested that, although clonidine at the administered dose did not reduce the frequency of headaches, it does significantly reduce severity of headaches in some patients and appears to reduce duration. The trial produced convincing evidence that in no respect were patients worse on clonidine than on placebo.

Study 3:

The efficacy of clonidine and propranolol in the prophylactic treatment of migraine has been evaluated in the following comparative, double-blind, crossover trial. Patients (n=21; 6M / 15F, aged 22-62 years) were administered propranolol and clonidine at a daily dose of 160 mg and 100µg, respectively, in a randomized sequence. Each period lasted 16 weeks. All patients recorded their migraine attacks on a diary card every 4 weeks. The attacks were graded from 1-4, according to the severity. A comparison of the pretreatment period of 4 weeks with the last 4 weeks of each evaluation period is shown in the table below. The first 4 weeks of each period were excluded from the final analysis.

Table 11: Results of treatment comparing pretreatment period with the last 4 weeks of treatment (headache days)

	Excellent/good (>50% reduction)	**Fair (<50% reduction)**	**Worse**	**Unchanged**
Propranolol	13 (62%)	3 (14%)	4 (19%)	1 (5%)
Clonidine	8 (38%)	9 (43%)	2 (10%)	2 (10%)

The results of the study show that 13 p atients (62%) had more than 50% reduction of headache days with propranolol treatment and eight patients (38 %) with clonidine treatment. When comparing the two drugs with respect to headache days, 10 patients had a better response on propranolol treatment, nine patients were better on clonidine treatment and there was no difference in two patients. The difference in headache days was very small in some patients and statistical analysis did not show any significant difference between clonidine and propranolol in migraine prophylaxis (Kåss B et al 1980).

Study 4:

A random double-blind placebo-controlled study was performed on 2 groups of 20 patients each to determine the effects of clonidine and mianserin on histamine-induced migraine and spontaneous attacks. The clinical history of migraine was longer than 5 years in both groups of patients. The first group (6M / 14F, aged 22-47.5 years) was affected by common migraine and the second (8M / 12F, aged 21-48 years) by tension headache. Clonidine 0.15 mg/per os/daily and mianserine 30 mg/per os/daily were administered for periods of 90 days each. Between successive treatments a 7 days' wash-out was performed. Histamine was used to induce migraine attacks in all patients. Before and after every treatment the threshold of histamine-induced migraine was evaluated. Induced-pain intensity showed a non-significant change after both treatments in the migraine group. In the tension headache group, clonidine treatment induced a non-significant decrease of pain intensity. The authors suggested that clonidine was able to decrease the functional tonus of the catecholaminergic system with a reduction of the migraine attack frequency, as well as their intensity and duration. This confirms the efficacy in preventing migraine attacks of drugs that inhibit the activity of the catecholaminergic system (Martucci N et al 1985).

Study 5:

In the following double-blind study, Sjaastad and colleagues enrolled 26 migraine patients (4M / 22F) to evaluate the effect of clonidine as a prophylactic remedy against migraine. Patients were randomized to clonidine 75µg/daily or placebo. A double-blind technique was employed, with each treatment period lasting 3 weeks. The efficacy of clonidine in reducing attacks of headache was evaluated on the basis of 4 different parameters: (1) average reduction in the number of headache days; (2) average reduction in headache indices (headache days times severity); (3) the number of patients in whom a 50 % reduction in headache indices was achieved; and (4) the number of patients markedly improved,

moderately improved, unchanged, and worse in terms of headache indices. A 50% reduction or more in headache indices was achieved in 10/26 patients (38%). A mean reduction of 27% in headache indices was brought about by clonidine ($P < 0.025$). In terms of headache days, a mean reduction of 26% was achieved with clonidine. Of the 26 patients, 13 experienced substantial improvement in headache indices and 3 moderate improvement, whereas 5 were unchanged and 5 worse when given clonidine; thus, a total of 16 of 26 (62%) managed better with clonidine than with placebo ($P < 0.025$). In conclusion, this study confirms that clonidine therapy has beneficial effects in migraine patients (Sjaastad O et al 1971).

Efficacy in vasomotor conditions associated with the menopause:

Study 1:

The following, placebo-controlled, double-blind, crossover study has shown clonidine to have a statistically highly significant effect in controlling the number and the severity and duration of menopausal flushes. Patients received tablets containing 25µg clonidine or placebo, beginning with one tablet twice daily (50µg/day) and increased to a maximum of three tablets twice daily (150µg/day), for nine weeks, with a one week washout period between treatments. The flushing attacks were recorded by the patient on a diary card and their answers to questions about the frequency, severity, and duration of attacks since the previous visit were recorded on a five-point scale from "much more" to "much less." Forty-two patients received clonidine first and 44 received placebo first. Treatment was affected for two weeks in one of the patients administered placebo as the first treatment. The missed weeks were not included in the analysis.

Table 12: Mean number of flushes in 42 patients who received clonidine first and 43* patients who received placebo first

Week:			**Mean**	**Mean change from initial value**	**S.D.**
Clonidine as first treatment	Initial		44.1	--	--
	Clonidine	1	36.6	-7.5	14.9
		2	25.9	-18.2	23.9
		3	24.6	-19.5	23.1
		4	25.0	-19.2	25.0
	Placebo	1	30.0	-14.2	19.5
		2	31.7	-12.5	19.8
		3	32.5	-11.7	21.0
		4	31.0	-13.1	23.3
Placebo as first treatment	Initial		50.2	--	--
	Placebo	1	45.1	-5.1	20.3
		2	36.7	-14.6	31.3
		3	32.1	-18.1	32.3
		4	33.5	-16.7	34.5
	Clonidine	1	28.1	-22.1	35.8
		2	24.7	-25.5	34.7
		3	24.6	-25.7	35.9
		4	22.1	-28.1	36.7

*One patient was excluded from this analysis because diary cards for two-weeks were incomplete.

For both groups of patients the reduction in the number of flushes throughout the period of clonidine treatment was significantly greater than the reduction during placebo treatment (clonidine before placebo P $\leq$0.05; clonidine after placebo P $\leq$0.001). The authors of the study concluded that clonidine, in doses similar to those used for migraine prophylaxis, seems to be a useful and safe alternative to other treatments for hot flushes (Clayden JR et al 1974).

Study 2:

Clayden JR 1972 conducted the following pilot study to evaluate the effect of clonidine on menopausal flushing. Eleven patients (aged 44 - 52 years; mean age: 46.3 years) with symptoms of menopausal flushing for 3 months to 5 years were enrolled. The study was carried out over a 6-week initial period, and the dosage adjusted at 2-week intervals, depending upon response. The dose of clonidine was in the same range as advocated in the treatment of migraine (0.025-0.075 mg twice daily). The response to treatment in patients with menopausal flushing treated with clonidine is presented in the table below.

Table 13: Results of the trial of clonidine in menopausal flushing

Patient no.	Age (years)	Duration of symptoms	Final clonidine dosage (mg)	Mean daily attack-rate pre-treatment	Mean daily attack-rate post-treatment
1	49	2 years	0.050 twice daily	7	0-1
2	49	6 months	0.025 twice daily	10	0-2
3	46	2 years	0.025 twice daily	8	0-1
4	49	6 months	0.50 twice daily	12	0-2
5	50	3.5 years	0.025 twice daily	15	15
6	49	3 months	0.050 twice daily	15	3-5
7	44	1 year	0.050 three times daily	10	1
8	52	4 months	0.050 twice daily	12	0-2
9	46	1 year	0.050 twice daily	9	3-4
10	49	6 months	0.075 twice daily	7	7
11	47	2 years	0.050 twice daily	6	0-1

Seven patients responded well to clonidine, with a reduction in attack-rate from as many as 15 per day to 1-2 per day. Two had a reasonable response with a similar reduction to about 4 per day and two patients did not respond at all. In all the cases that responded, the drug gradually reduced the attack-rate until the optimum dose was reached, with the optimum dose varying in each case. All patients who responded demonstrated a decrease in intensity and duration of attacks as well as a reduction in number of attacks. Over half the patients were followed for 3 to 6 months and had maintained their initial improvement with no need to

increase the dose. Hence, it seems that clonidine fulfils the criterion of an effective remedy for menopausal flushing.

Study 3:

Schindler AE et al 1979 conducted a study with clonidine in menopausal women. Eleven women with menopausal symptoms (mean age: 50.9 years; age range: 34 - 68 years) were treated with clonidine 150µg/daily given in three divided doses. Before and during therapy, plasma estradiol-17β, LH (Luteinizing Hormone), FSH (Follicle Stimulating Hormone) and prolactin levels were measured by specific radio-immunoassays. In addition, the number of hot flushes a day and symptoms were monitored by the Kupperman-index. A highly significant fall in the number of hot flushes by day and night occurred during therapy ($P<0.001$), and the Kupperman-index similarly improved. These changes were independent of differences in plasma hormone values. No significant changes in pulse and blood pressure changes were noted and plasma hormone concentrations remained unchanged. The authors concluded that clonidine appears to be the treatment of choice for menopausal symptoms.

Study 4:

Clonidine, 0.05 mg twice daily, was evaluated in a m ulticentre, randomized, placebo-controlled, double-blind crossover study in 66 patients (56 menopausal patients and 10 women whose ovaries had been removed; age range: 27 - 71 years) who had had menopausal flushing for less than 1 year. The study consisted of four separate trials, two conducted by the same investigator. A randomized, placebo-controlled, double-blind, crossover design was used. In each trial 0.05 mg of clonidine or a placebo that looked identical was given twice a day for 4 weeks, then the alternate drug was given at the same dosage for 4 weeks; the order of administration was randomized. In trial 3 a 4-week, single-blind placebo period immediately preceded and immediately followed the test period; data from the additional placebo periods were not considered in the statistical evaluation. Each patient kept a diary of the time, extent, severity and duration of flushing. At each visit the patient was interviewed, and her vital signs were recorded. The mean number of flushing attacks in the first 14 days after crossover to the alternate therapy is presented below. There was no significant variation in the response to clonidine between the four trials; therefore, the findings were averaged.

Table 14: Mean number of flushing attacks in the first 14 days after crossover to the alternate therapy.

Drug	Mean no. of attacks (and no. of patients)				
	Trial 1 (n=20)	Trial 2 (n=17)	Trial 3 (n=20)	Trial 4 (n=9)	Overall (n=66)
Clonidine	42.1	64.2	76.5	31.6	56.8
Placebo	42.3	74.1	85.1	48.0	64.3
Difference	0.2	9.9	8.6	16.4	7.5*
Standard error	7.44	8.10	4.16	6.65	3.43

*Significant at P<0.05 (paired t-test)

The mean number of flushing attacks in the first 14 days after crossover to the alternate therapy was 64.3 with placebo therapy but only 56.8 with clonidine therapy, a significant difference (P < 0.05; paired t-test). The following significant changes occurred after crossover: the frequency of flushing was lower in 21 (78%) of 27 patients crossed over to clonidine and in 15 (50%) of 30 patients crossed over to placebo; the severity of the attacks was reduced in 24 (89%) of 27 patients crossed over to clonidine and in 16 (53%) of 30 patients crossed over to placebo; and the attacks were shorter in 23 (88%) of 26 patients crossed over to clonidine and in 14 (50%) of 28 patients crossed over to placebo. The available evidence indicates that clonidine, by virtue of its ability to stabilize the peripheral vasculature, is potentially useful for the treatment of menopausal flushing (Edington RF et al 1980).

Study 5:

Breast cancer patients with treatment-induced menopause experience frequent and severe hot flashes (HF). In the following double-blind, cross-over study, Buijs and colleagues compared the efficacy of venlafaxine and clonidine for the treatment of HF in breast cancer patients. Patients experiencing HF were randomized to 8 weeks venlafaxine followed by 2 weeks wash-out, and 8 weeks clonidine or vice versa (venlafaxine: n=43; and clonidine: n=47). HF frequency and severity were assessed. With both drugs the hot flash scores were reduced with a median of 49% for venlafaxine and 55% for clonidine after 8 weeks. No difference in hot flash reduction was seen between the two drugs (P =0 .55). A complete disappearance of hot flashes was seen in 4 patients during venlafaxine, but not on clonidine. Fifty percent of the patients on venlafaxine and 55% of the patients on clonidine reported a ≥50% reduction in

hot flash score after 8 weeks. Conclusively, this study demonstrates that venlafaxine and clonidine have similar efficacy. Hence, venlafaxine and clonidine are equally good alternatives for the prevention of hot flashes in breast cancer patients (Buijs C et al 2009).

2.5.5 Overview of Safety

Adverse Events Profile

Most adverse effects are mild and tend to diminish with continued therapy. Adverse events have been ranked under headings of frequency using the following convention (SmPC-Dixarit, 2014):

Very common	≥ 1/10
Common	≥ 1/100, <1/10
Uncommon	≥1/1000, <1/100
Rare	≥1/10000, <1/1000
Very rare	<1/10000
Not known	Cannot be estimated from the available data

Table 15: Adverse Events Profile of Clonidine

Organ system	Frequency	Adverse effects
Endocrine disorders	Rare	Gynaecomastia
Psychiatric disorders	Common	Depression, sleep disorder
	Uncommon	Delusional perception, hallucination, nightmare
	Not known	Confusional state, libido decreased
Nervous system disorders	Very common	Dizziness, sedation
	Common	Headache
	Uncommon	Paraesthesia
Eye disorder	Rare	Lacrimation decreased
	Not known	Accommodation disorder
Cardiac disorders	Uncommon	Sinus bradycardia
	Rare	Atrioventricular block
	Not known	Bradyarrhythmia
Vascular disorders	Very common	Orthostatic hypotension
	Uncommon	Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Rare	Nasal dryness
Gastrointestinal disorders	Very common	Dry mouth
	Common	Constipation, nausea, salivary gland pain, vomiting
	Rare	Colonic pseudo-obstruction
Skin and subcutaneous tissue disorders	Uncommon	Pruritus, rash, urticaria
	Rare	Alopecia
Reproductive system and breast disorders	Common	Erectile dysfunction
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Malaise
Investigations	Rare	Blood glucose increased

Clonidine treatment is generally well tolerated (Buijs C et al 2009 and Houston MC 1981). The main side-effects of clonidine are related to its pharmacological actions as an alpha adrenoceptor agonist. The frequency and severity of two most common adverse reactions of clonidine, sedation and dry mouth are reported to be dose related (Keränen A et al 1978 and Anavekar SN et al 1982).

A review discussing the frequency of adverse reactions to clonidine reported that the vast majority of patients (93%) tolerate the drug satisfactorily. Only 7% of patients discontinued clonidine due to intolerable side effects. The most common side effects are sedation and dry mouth, which are usually mild and tend to diminish or disappear within 2-4 weeks of continued administration. Long-term studies have shown few to no adverse effects after 6 months to 5 years of clonidine use. As the majority of side effects are dose and time related, studies using unusually high doses or too rapid dose increases might have essentially overestimated some of the more frequent adverse effects. Sedation and dry mouth can be minimized by starting therapy with small doses of 0.1 mg each night and then slowly increasing by 0.1 mg each week, with the larger portion of the daily dose being given at bedtime. In a group of patients receiving clonidine, there was a complete absence of any sign of drug-related eye damage after 5 years of treatment. Clonidine does not significantly alter glucose tolerance in the diabetic patient unlike thiazide diuretics and other antihypertensives (Houston MC 1981).

In the dose range 25 - 75 µg twice daily, clonidine shows relatively mild side effects and does not show any potentially harmful oestrogenic effects, suggesting that is a useful alternative to the existing therapy for menopausal flushing (Clayden JR et al 1974).

The most commonly reported side effects during continuous administration of clonidine 75 - 150µg daily have been drowsiness, dryness of the mouth and anxiety or depression. These effects tend to reduce as treatment continues. The total incidence of side-effects is generally about 15 - 25%, and the cessation of treatment has rarely been required. An accompanying reduction in the frequency of hot flushes with clonidine has been reported in menopausal women during migraine prophylaxis. A fall in blood pressure was reported in some studies, but hypotension has not been reported at the dosage used in migraine prophylaxis (Brogden RN et al 1975).

Rare cases of hyperprolactinemia, gynecomastia and galactorrhea have been reported after clonidine administration (Mendhekar DN 2005, Heim J et al 1979 and Lactmed 2015).

Effects on Ability to Drive and Use Machines

Clonidine was found to induce deleterious effects in psychometric tests and in EEG (electroencephalogram) analysis (Denolle T et al 2002). No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as dizziness, sedation and accommodation disorder during treatment with clonidine. If patients experience any of these side effects they should avoid potentially hazardous tasks such as driving or operating machinery (SmPC-Dixarit, 2014).

Post-marketing Surveillance

Clonidine showed minimum side effects during 10-years of therapy in 128 patients (60M / 68F; aged 40 ± 9 years) (Ferder L et al 1987).

In a 10-year retrospective, explorative analysis in young children (0–6 years of age), there were no severe (Poisoning Severity Score [PSS] = 3) or fatal poisonings (PSS = 4) reported following the administration of clonidine (Hetterich N et al 2014).

A retrospective analysis of data over a 6 year period and a total of 10060 reported exposures showed that most clonidine exposures resulted in minimal toxic effects. Most exposures resulted in no effect (40%) or minor effects (39%). Moderate effects occurred in 19%, major effects in 2%; there was 1 fatality in a 23-month-old (Klein-Schwartz W 2002).

Dosage and Administration (SmPC-Dixarit, 2014).

Adults:

Initially 50 micrograms twice daily. If after two weeks there has been no remission, increase to 75 micrograms twice daily.

The duration of treatment depends upon the severity of the condition.

If symptoms continue to occur, the patient should be informed that it may take 2 - 4 weeks until clonidine is fully effective.

Elderly:

No specific information on the use of this product in the elderly is available.

Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

Paediatric Population:

There is insufficient evidence for the application of clonidine in children and adolescents younger than 18 years. Therefore the use of clonidine is not recommended in paediatric subjects under 18 years.

Patients with renal impairment

Clonidine should be used with caution in patients with renal insufficiency. Careful monitoring of blood pressure is required.

Use in Pregnancy, Lactation and Fertility

Pregnancy

Data regarding the use of clonidine in pregnant women is limited. As with all medicines, clonidine should not be used in pregnancy, especially the first trimester, unless the expected benefit is thought to outweigh any possible risk to the foetus (SmPC-Dixarit, 2014).

Clonidine passes the placental barrier and may lower the heart rate of the foetus. Concentrations were equal in maternal serum and umbilical cord serum. No adverse effects on blood glucose, electrocardiogram or blood pressure were seen during the first 3 days postpartum of the infants and they had normal growth and psychomotor development at 1 year of age (Boutroy MJ 1989, Hartikainen-Sorri AL et al 1987, Buchanan ML et al 2009 and Rothberger S et al 2010). However, postpartum a transient rise in blood pressure in the newborn cannot be excluded (SmPC-Dixarit, 2014).

No teratogenic effects have been reported in clinical practice or in animals. Clonidine does not seem to be deleterious for foetal growth, mortality and morbidity (Boutroy MJ 1989, Hartikainen-Sorri AL et al 1987, Buchanan ML et al 2009 and Rothberger S et al 2010). In animal studies involving doses higher than the equivalent maximum therapeutic dose in man,

effects on foetal development were only seen in one species. Foetal malformations did not occur. There is no adequate experience regarding the long-term effects of prenatal exposure; therefore, careful monitoring of the mother and child is recommended (SmPC-Dixarit, 2014).

Lactation

Clonidine is excreted in human milk. However, there is insufficient information on the effect on newborns. The use of clonidine is therefore not recommended during breast feeding (SmPC-Dixarit, 2014).

Clonidine concentrations in milk were reported to be roughly twice that in maternal serum; in the serum of the newborns the concentrations were about half those of the mothers. All concentrations corresponded well to the doses of the drug (Sevrez C et al 2014 and Hartikainen-Sorri AL et al 1987). No typical clonidine side effects (e.g., dry mouth, sedation) were seen in 9 infants whose mothers were taking clonidine, despite the infants' serum levels being about two-thirds that of their mothers'.

A case study reported the effects of clonidine on an infant born to a mother taking clonidine 0.15 mg daily during pregnancy and postpartum. At 2 days of life, the infant presented with drowsiness, hypotonia, and suspected generalized seizures. However, on day 9 postpartum, breastfeeding was stopped and all symptoms resolved within 24 hours (Lactmed 2015).

Fertility

No clinical studies on t he effect on human fertility have been conducted with clonidine. However, non-clinical studies with clonidine indicate no direct or indirect harmful effects with respect to the fertility index (SmPC-Dixarit, 2014).

A pilot study has reported the effects of clonidine on sexual function in pre- and post-menopausal women found that clonidine affected some aspects of sexual functioning, including urge and strength (Hodge RH et al 1991). However, in a study by Buijs C et al 2009, no effect on sexual functioning was found with clonidine treatment.

Overdose

Symptoms:

Manifestations of intoxication are due to generalised sympathetic depression and include papillary constriction, somnolence including coma, hypotension, orthostatic hypotension, bradycardia, hypothermia, respiratory depression including apnoea, occasionally vomiting, very occasionally hypertension and dryness of the mouth (SmPC-Dixarit, 2014; Seger DL 2002 and Anderson RJ et al 1981).

Treatment:

There is no specific antidote for clonidine overdose. Administration of activated charcoal should be performed where appropriate. Supportive care may include atropine sulfate for symptomatic bradycardia, and intravenous fluids and/or inotropic sympathomimetic agents for hypotension. Severe persistent hypertension may require correction with alpha-adrenoceptor blocking drugs. Naloxone may be a useful adjunct for the management of clonidine-induced respiratory depression (SmPC-Dixarit, 2014; Hansson L et al 1973 and Eddy O et al 2003).

2.5.6 Benefits and Risks Conclusion

Clonidine hydrochloride 50micrograms/5ml Sugar Free Oral Solution is indicated for the prophylactic management of migraine or recurrent vascular headache, and the management of vasomotor conditions commonly associated with menopause and characterised by flushing. Clonidine is an α-adrenergic agent that appears to act on bo th peripheral and central structures. Treatment with clonidine diminishes the responsiveness of peripheral vessels to constrictor and dilator stimuli, thereby preventing the vascular changes associated with migraine. The same direct action on peripheral vessels moderates the vascular changes associated with menopausal flushing.

The pharmacokinetics of clonidine are dose-proportional in the range of 75-300 micrograms. Clonidine undergoes a minor first pass effect and is highly absorbed with 75 - 100 % bioavailability. It has a plasma protein binding of 30-40 % and is rapidly and extensively distributed into tissues. Clonidine crosses the blood-brain barrier, as well as the placental barrier, and is found in human milk. At least 4 metabolites of clonidine have been detected in human urine. The main metabolite p-hydroxy-clonidine is pharmacologically inactive. About 70 % of the dose administered is excreted with the urine mainly in the form of the unchanged parent drug (40-60 % of the dose) which is reportedly independent of the administered dose, formulation, or the mode of administration. Approximately 20% of the total amount is excreted with the faeces, out of which about 15% i s unchanged drug. The terminal elimination half-life of clonidine has been found to range from 5 t o 25.5 hours. It can be prolonged to up to 41 hours in patients with severely impaired renal function. There is no definitive data about food or race effects on the pharmacokinetics of clonidine.

The efficacy and safety of clonidine for its proposed indications has been studied in several clinical trials. These clinical studies have demonstrated the efficacy of clonidine for the treatment and prophylaxis of migraine and flushing. Clonidine treatment is generally well tolerated. The main side-effects of clonidine are related to its pharmacological actions as an alpha adrenoceptor agonist. The frequency and severity of two most common adverse reactions of clonidine, sedation and dry mouth, are reported to be dose related. Most adverse effects are mild and tend to diminish with continued therapy. Patients should avoid potentially hazardous tasks such as driving or operating machinery if they experience undesirable effects such as dizziness, sedation and accommodation disorder during treatment

with clonidine. Clonidine is known to pass the placental barrier and may lower the heart rate of the foetus; therefore it should not be used in pregnancy, especially the first trimester, unless the expected benefit is thought to outweigh any possible risk to the foetus. Clonidine is excreted in human milk. However, there is insufficient information on the effect on newborns. The use of clonidine is therefore not recommended during breast feeding. No clinical studies on the effect on human fertility have been conducted with clonidine. However, non-clinical studies with clonidine indicate no direct or indirect harmful effects with respect to the fertility index. These data suggest that clonidine is effective for its proposed indications, with the advantage of a good safety profile.

This marketing authorisation application is made in accordance with Article 10(1) on the basis that the proposed product Clonidine hydrochloride 50micrograms/5ml Sugar Free Oral Solution is essentially similar to the reference product Dixarit Tablets 25 micrograms of Boehringer Ingelheim Limited. No new clinical studies have been performed by the applicant as additional studies will not add any new information to the knowledge gained through wide spread clinical use of over 30 years. Since the proposed Clonidine hydrochloride 50micrograms/5ml Sugar Free Oral Solution is a generic product it will offer an additional cost advantage over the existing branded products. An oral solution will also ease the administration of drug to patient populations who cannot easily swallow solid dosage forms such as tablets. The proposed indications and dosages of Clonidine hydrochloride 50micrograms/5ml Sugar Free Oral Solution are the same as those of the reference product. Therefore, the medical benefits and risks from the proposed product would be the same as that of the reference product.

2.5.7 Literature References

1. Abo-Zena RA, Bobek MB and Dweik RA. Hypertensive urgency induced by an interaction of mirtazapine and clonidine. Pharmacotherapy 2000; 20(4): 476-478.
2. Adam EI, Gore SM and Price WH. Double blind trial of clonidine in the treatment of migraine in a general practice. J R Coll Gen Pract 1978; 28(195): 587-590.
3. Affrime MB, Lowenthal DT and Rufo M. Failure of rifampin to induce the metabolism of clonidine in normal volunteers. Drug Intell Clin Pharm 1981; 15(12): 964-966.
4. Anavekar SN, Howes LG and Jarrott B et al. Pharmacokinetics and antihypertensive effects of low dose clonidine during chronic therapy. J Clin Pharmacol 1989; 29(4): 321-326.
5. Anavekar SN, Jarrott B and Toscano M et al. Pharmacokinetic and pharmacodynamic studies of oral clonidine in normotensive subjects. Eur J Clin Pharmacol 1982; 23(1): 1-5.
6. Anderson JR and Nawarskas JJ. Cardiovascular drug-drug interactions. Cardiol Clin 2001; 19(2): 215-234.
7. Anderson RJ, Hart GR and Crumpler CP et al. Clonidine overdose: report of six cases and review of the literature. Ann Emerg Med 1981; 10(2): 107-112.
8. Arenas-López S, Riphagen S and Tibby SM et al. Use of oral clonidine for sedation in ventilated paediatric intensive care patients. Intensive Care Med 2004; 30(8): 1625-1629.
9. Arndts D, Doevendans J and Kirsten R et al. New aspects of the pharmacokinetics and pharmacodynamics of clonidine in man. Eur J Clin Pharmacol 1983; 24(1): 21-30.
10. Arndts D. New aspects of the clinical pharmacology of clonidine. Chest 1983; 83(2 Suppl): 397-400.
11. Beckett AH, Behrendt WA and Hadzija BW. Some aspects on the bioavailability of a controlled release clonidine formulation in man. Int J Biol Pharm Allied Sci 1989; 52(1): 37-45.
12. Boswell G, Bekersky I and Mekki Q et al. Plasma concentrations and disposition of clonidine following a constant 14-day epidural infusion in cancer patients. Clin Ther 1997; 19(5): 1024-1030.
13. Boutroy MJ, Gisonna CR and Legagneur M. Clonidine: placental transfer and neonatal adaption. Early Hum Dev 1988; 17(2-3): 275-286.

14. Boutroy MJ. Fetal effects of maternally administered clonidine and angiotensin converting enzyme inhibitors. Dev Pharmacol Ther 1989; 13(2-4): 199-204.
15. Brogden RN, Pinder RM and Sawyer PR et al. Low-dose clonidine: a review of its therapeutic efficacy in migraine prophylaxis. Drugs 1975; 10(5-6): 357-365.
16. Buchanan ML, Easterling TR and Carr DB et al. Clonidine pharmacokinetics in pregnancy. Drug Metab Dispos 2009; 37(4): 702-705.
17. Buijs C, Mom CH and Willemse PH et al. Venlafaxine versus clonidine for the treatment of hot flashes in breast cancer patients: a double-blind, randomized cross-over study. Breast Cancer Res Treat 2009; 115(3): 573-580.
18. Claessens AJ, Risler LJ and Eyal S et al. CYP2D6 mediates 4-hydroxylation of clonidine in vitro: implication for pregnancy-induced changes in clonidine clearance. Drug Metab Dispos 2010; 38(9): 1393-1396.
19. Clayden JR, Bell JW and Pollard P. Menopausal flushing: double-blind trial of a non-hormonal medication. Br Med J 1974; 1(5905): 409-412.
20. Clayden JR. Effect of clonidine on menopausal flushing. Lancet 1972; 2(7791): 1361-1361.
21. Cunningham FE, Baughman VL and Peters J et al. Comparative pharmacokinetics of oral versus sublingual clonidine. J Clin Anesth 1994; 6(5): 430-433.
22. Darda S, Förster HJ and Sthle H. [Metabolic degradation of clonidine (author's transl)]. Arzneimittelforschung 1978; 28(2): 255-259.
23. Davies DS, Wing AM and Reid JL et al. Pharmacokinetics and concentration-effect relationships of intervenous and oral clonidine. Clin Pharmacol Ther 1977; 21(5): 593-601.
24. Daviss WB, Patel NC and Robb AS et al. Clonidine for attention-deficit/hyperactivity disorder: II. ECG changes and adverse events analysis. J Am Acad Child Adolesc Psychiatry 2008; 47(2): 189-198.
25. Denolle T, Sassano P and Allain H et al. Effects of nicardipine and clonidine on cognitive functions and electroencephalography in hypertensive patients. Fundam Clin Pharmacol 2002; 16(6): 527-535.
26. Dowty ME and Dietsch CR. Improved prediction of in vivo peroral absorption from in vitro intestinal permeability using an internal standard to control for intra- and inter-rat variability. Pharm Res 1997; 14(12): 1792-1797.
27. Eddy O and Howell JM. Are one or two dangerous? Clonidine and topical imidazolines exposure in toddlers. J Emerg Med 2003; 25(3): 297-302.

28. Edington RF, Chagnon JP and Steinberg WM. Clonidine (Dixarit) for menopausal flushing. Can Med Assoc J 1980; 123(1): 23-26.
29. EMIS, Egton Medical Information Systems Limited, Hot Flushes, 2015.
30. EMIS, Egton Medical Information Systems Limited, Migraine, 2014.
31. Faassen F, Vogel G and Spanings H et al. Caco-2 permeability, P-glycoprotein transport ratios and brain penetration of heterocyclic drugs. Int J Pharm 2003; 263(1-2): 113-122.
32. Ferder L, Inserra F and Medina F. Safety aspects of long-term antihypertensive therapy (10 years) with clonidine. J Cardiovasc Pharmacol 1987; 10 Suppl 12: S104-108.
33. Freedman RR and Dinsay R. Clonidine raises the sweating threshold in symptomatic but not in asymptomatic postmenopausal women. Fertil Steril 2000; 74(1): 20-23.
34. Frisk-Holmberg M, Edlund PO and Paalzow L. Pharmacokinetics of clonidine and its relation to the hypotensive effect in patients. Br J Clin Pharmacol 1978; 6(3): 227-32.
35. Frisk-Holmberg M, Paalzow L and Edlund PO. Clonidine kinetics in man--evidence for dose dependency and changed pharmacokinetics during chronic therapy. Br J Clin Pharmacol 1981; 12(5): 653-658.
36. Ginsburg J and O'Reilly B. Effect of oral clonidine on the vascular effects of stressful mental arithmetic in menopausal women. J Cardiovasc Pharmacol 1987; 10 Suppl 12: S138-141.
37. Ginsburg J, O'Reilly B and Swinhoe J. Effect of oral clonidine on human cardiovascular responsiveness: a possible explanation of the therapeutic action of the drug in menopausal flushing and migraine. Br J Obstet Gynaecol 1985; 92(11): 1169-1175.
38. Glynn CJ, Jamous MA and Teddy PJ. Cerebrospinal fluid kinetics of epidural clonidine in man. Pain 1992; 49(3): 361-367.
39. Hansson L, Hunyor SN and Julius S et al. Blood pressure crisis following withdrawal of clonidine (Catapres, Catapresan), with special reference to arterial and urinary catecholamine levels, and suggestions for acute management. Am Heart J 1973; 85(5): 605-610.
40. Hartikainen-Sorri AL, Heikkinen JE and Koivisto M. Pharmacokinetics of clonidine during pregnancy and nursing. Obstet Gynecol 1987; 69(4): 598-600.
41. Heim J, Massart C and Auvray E et al. [Post-partum galactorrhea with hyperprolactinaemia persistent during a clonidine treatment (author's transl)]. Sem Hop 1979; 55(41-42): 1933-1934.

42. Hetterich N, Lauterbach E a nd Stürer A et al. Toxicity of antihypertensives in unintentional poisoning of young children. J Emerg Med 2014; 47(2): 155-162.
43. Hodge RH, Harward MP and West MS et al. Sexual function of women taking antihypertensive agents: a comparative study. J Gen Intern Med 1991; 6(4): 290-294.
44. Hogan MJ, Wallin JD and Chu LC. Plasma clonidine concentration and pharmacologic effect. Clin Pharmacol Ther 1981; 30(6): 729-734.
45. Houston MC. Clonidine hydrochloride: review of pharmacologic and clinical aspects. Prog Cardiovasc Dis 1981; 23(5): 337-350.
46. Itskovitz HD. Clonidine and the kidney. J Cardiovasc Pharmacol 1980; 2 Suppl 1: S47-60.
47. Jarrott B, Conway EL and Maccarrone C et al. Clonidine: understanding its disposition, sites and mechanism of action. Clin Exp Pharmacol Physiol 1987; 14(5): 471-479.
48. Kåss B and Nestvold K. Propranolol (Inderal) and clonidine (Catapressan) in the prophylactic treatment of migraine. A comparative trial. Acta Neurol Scand 1980; 61(6): 351-356.
49. Keränen A, Nykänen S and Taskinen J. Pharmacokinetics and side-effects of clonidine. Eur J Clin Pharmacol 1978; 13(2): 97-101.
50. Klein-Schwartz W. Trends and toxic effects from pediatric clonidine exposures. Arch Pediatr Adolesc Med 2002; 156(4): 392-396.
51. LactMed Record Number 73, Clonidine, 2015.
52. Larsson P, Nordlinder A and Bergendahl HT et al. Oral bioavailability of clonidine in children. Paediatr Anaesth 2011; 21(3): 335-340.
53. Lowenthal DT, Affrime MB and Meyer A et al. Pharmacokinetics and pharmacodynamics of clonidine in varying states of renal function. Chest 1983; 83(2 Suppl): 386-390.
54. Lowenthal DT, Matzek KM and MacGregor TR. Clinical pharmacokinetics of clonidine. Clin Pharmacokinet 1988; 14(5): 287-310.
55. Lowenthal DT. Pharmacokinetics of clonidine. J Cardiovasc Pharmacol 1980; 2 Suppl 1: S29-37.
56. Martucci N, Manna V and Porto C et al. Migraine and the noradrenergic control of vasomotricity: a study with alpha-2 stimulant and alpha-2 blocker drugs. Headache 1985; 25(2): 95-100.
57. Mendhekar DN. Clonidine-induced gynecomastia and hyperprolactinemia in a 6-year-old child. J Clin Psychiatry 2005; 66(12): 1616-1617.

58. Onesti G, Schwartz AB and Kim KE et al. Antihypertensive effect of clonidine. Circ Res 1971; 28(5): Suppl 2: 53-69.

59. Palumbo DR, Sallee FR and Pelham WE Jr et al. Clonidine for attention-deficit/hyperactivity disorder: I. Efficacy and tolerability outcomes. J Am Acad Child Adolesc Psychiatry 2008; 47(2): 180-188.

60. Pontier C, Pachot J and Botham R et al. HT29-MTX and Caco-2/TC7 monolayers as predictive models for human intestinal absorption: role of the mucus layer. J Pharm Sci 2001; 90(10): 1608-1619.

61. Potts AL, Larsson P and Eksborg S et al. Clonidine disposition in children; a population analysis. Paediatr Anaesth 2007; 17(10): 924-933.

62. Rothberger S, Carr D and Brateng D et al. Pharmacodynamics of clonidine therapy in pregnancy: a heterogeneous maternal response impacts fetal growth. Am J Hypertens 2010; 23(11): 1234-1240.

63. Schiller LR, Santa Ana CA and Morawski SG et al. Studies of the antidiarrheal action of clonidine. Effects on motility and intestinal absorption. Gastroenterology 1985; 89(5): 982-988.

64. Schindler AE, Müller D and Keller E et al. Studies with clonidine (dixarit) in menopausal women. Arch Gynecol 1979; 227(4): 341-347.

65. Schmitt H. The pharmacology of clonidine and related products. InAntihypertensive agents, Springer Berlin Heidelberg 1977; 299-396.

66. Schwartz JB. The influence of sex on pharmacokinetics. Clin Pharmacokinet 2003; 42(2): 107-121.

67. Seger DL. Clonidine toxicity revisited. J Toxicol Clin Toxicol 2002; 40(2): 145-155.

68. Sevrez C, Lavocat MP and Mounier G et al. Intoxication transplacentaire ou par lait maternel à la clonidine: un cas de somnolence et d'hypotonie néonatale. Archives de pédiatrie. 2014; 21(2): 198-200.

69. Shafar J, Tallett ER and Knowlson PA. Evaluation of clonidine in prophylaxis of migraine. Double-blind trial and follow-up. Lancet 1972; 1(7747): 403-407.

70. Sjaastad O and Stensrud P. 2-(2.6-dichlorophenylamino)-2-imidazoline hydrochloride (ST 155 or Catapresan) as a prophylactic remedy against migraine. Acta Neurol Scand 1971; 47(1): 120-122.

71. Summary of product characteristics, Dixarit Tablets 25 micrograms, Boehringer Ingelheim Limited, 2014.

72. Toxnet, Clonidine, 2012.

73. Varma MV, Sateesh K and Panchagnula R. Functional role of P-glycoprotein in limiting intestinal absorption of drugs: contribution of passive permeability to P-glycoprotein mediated efflux transport. Mol Pharm 2005; 2(1): 12-21.

74. Wing LM, Reid JL and Davies DS et al. Pharmacokinetic and concentration-effect relationships of clonidine in essential hypertension. Eur J Clin Pharmacol 1977; 12(6): 463-469.

75. Xie HG, Cao YJ and Gauda EB et al. Clonidine clearance matures rapidly during the early postnatal period: a population pharmacokinetic analysis in newborns with neonatal abstinence syndrome. J Clin Pharmacol 2011; 51(4): 502-511.