WHAT'S NEW IN THERAPEUTICS ?

SADECK VAWDA

MEDICAL UPDATE GROUP

October 2014

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DAPAGLIFLOZIN

A NEW CLASS OF ANTIDIABETIC AGENT

DAPAGLIFLOZIN

- **FIRST SODIUM – GLUCOSE CO-TRANSPORTER 2 INHIBITOR**
- **NOVEL INSULIN – INDEPENDENT MODE OF ACTION THAT TARGETS THE KIDNEY**

DAPAGLIFLOZIN

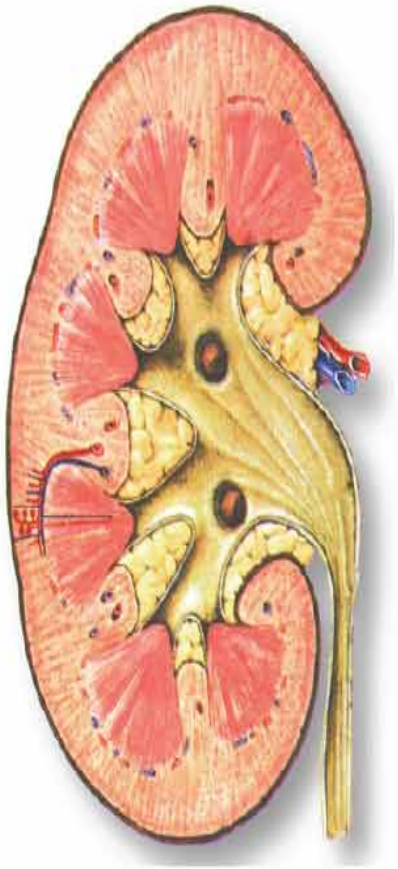
MECHANISM OF ACTION

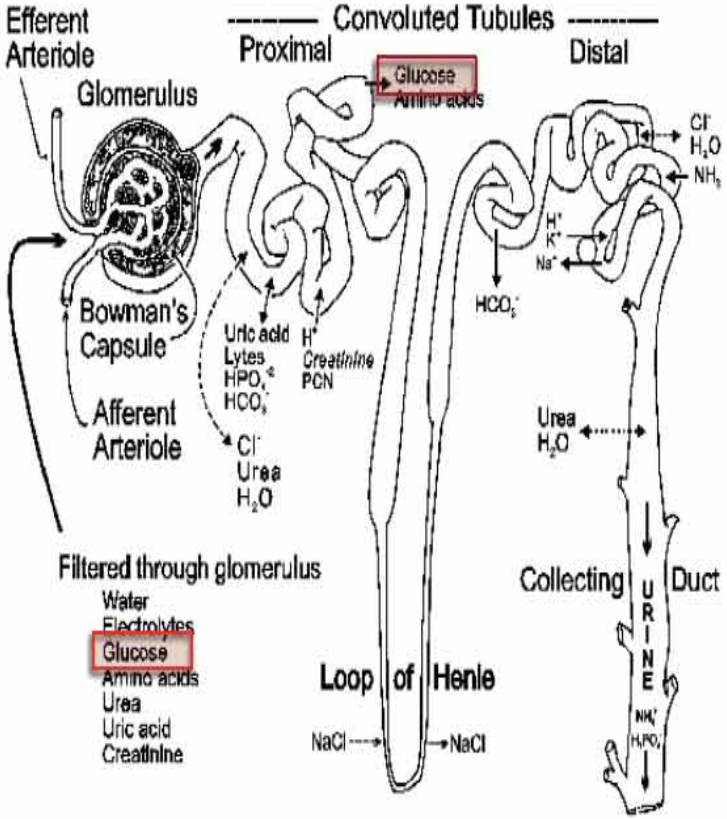
- THE POSSIBILITY OF ALTERING PLASMA GLUCOSE BY MODIFYING RENAL EXCRETION ORIGINATED FROM THE DISCOVERY OF PHLORIZIN.

- ALTHOUGH THE MOLECULE COULD NOT BE DEVELOPED AS A MEDICINE, IT WAS SHOWN TO NORMALISE FASTING AND FED GLUCOSE LEVELS IN DIABETIC RATS.

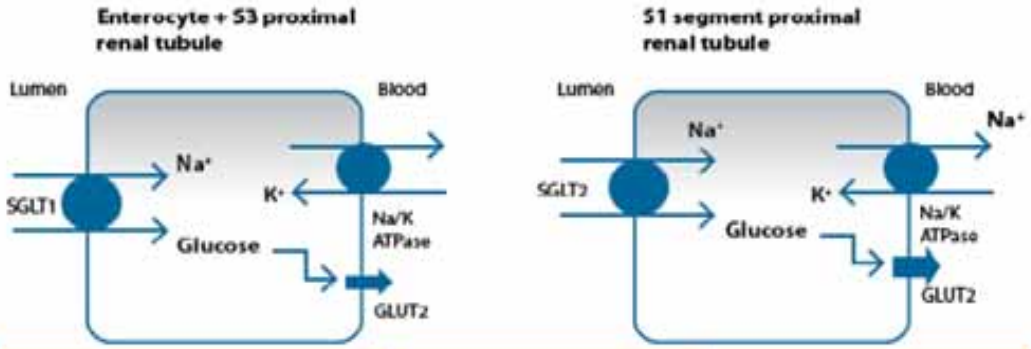
- GLUCOSE IS USUALLY FILTERED IN THE KIDNEY AND REABSORBED VIA ACTIVE TRANSPORT BY SGLT1 AND SGLT2. THE LATTER IS A HIGH CAPACITY, LOW AFFINITY CARRIER RESPONSIBLE FOR 90% OF REABSORBED GLUCOSE.

DAPAGLIFLOZIN





DAPAGLIFLOZIN



Récepteur	SGLT1	SGLT2
Localisation	Intestin Rein Coeur	Rein
Segment rénal	Fin de Tube contourné proximal	Début de Tube contourné proximal
Affinité pour le Glucose	Km = 0,4mM	Km = 2mM
Capacité de transport de glucose	Faible	Elevée
Taux de réabsorption du Glucose	10%	90%

- SGLT3: joue le rôle de glucose sensor au niveau de la membrane plasmique des neurones cholinergiques.
- SGLT4,5,6: non spécifique du transport du D-glucose. Rôle moins établit.

DAPAGLIFLOZIN

MECHANISM OF ACTION

- WHEN SGLT2 IS BLOCKED BY DAPAGLIFLOZIN, SOME OF THE FILTERED GLUCOSE IS EXCRETED IN THE URINE
- AS WELL AS DECREASING BLOOD GLUCOSE LEVELS, THIS MAY CAUSE MODERATE WEIGHT LOSS AND A SLIGHT DECREASE IN BLOOD PRESSURE
- OSMOTIC DIURESIS IS BELIEVED TO CONTRIBUTE TO THESE SECONDARY EFFECTS, ALTHOUGH THE WEIGHT LOSS IS POSSIBLY MAINTAINED BY FAT MASS REDUCTION DUE TO GLUCOSURIA

DAPAGLIFLOZIN

LICENSING

- IS APPROVED IN THE EUROPEAN UNION FOR TYPE 2 DIABETES AS MONOTHERAPY IN PATIENT INTOLERANT OF METFORMIN AND IN COMBINATION WITH SEVERAL OTHER ANTIDIABETIC AGENTS INCLUDING INSULIN

- RECOMMENDED DOSE IS 10mg ONCE DAILY WITH OR WITHOUT FOOD (MEANING IT CAN BE TAKEN AT A TIME THAT SUITS THE PATIENT).

DAPAGLIFLOZIN

EVIDENCE

- MARKETING AUTHORISATION WAS GRANTED BASED ON AN EXTENSIVE CLINICAL DEVELOPMENT PROGRAMME CONSISTING OF 12 PHASE III TRIALS

- THE MEAN REDUCTION IN HBAIC THROUGHOUT THE DEVELOPMENT PROGRAMME WAS CONSISTENTLY SIGNIFICANT AND RANGE FROM 0.4% TO 0.8% (AT 24 WEEKS)

- THIS IS SIMILAR TO THAT ACHIEVED BY PROGLITAZONE AND DPP4 INHIBITORS

DAPAGLIFLOZIN

Box 1: Summary of key trials

STUDY	DESCRIPTION	LIMITATIONS	KEY FINDINGS	CLINICAL SIGNIFICANCE/PRACTICAL NOTES
Nauck *et al*[3]	Add-on to metformin; dapagliflozin (2.5–10mg) versus sulphonylurea (glipizide 5–20mg/day)	Non-inferiority design therefore unable to prove that it is clinically better than sulphonylurea Patients were allowed treatment with another oral antidiabetic at half maximal dose (triple therapy) but no further details given	Both dapagliflozin and glipizide reduced HbA_{1c} by 0.52% but with different profiles of glucose alteration	Equivalent efficacy to glipizide as second-line therapy Showed weight loss versus weight gain with sulphonylurea, which may indicate a place in therapy for patients with higher BMI Significant reduction in hypoglycaemic events compared with sulphonylurea
Jabbour *et al*[5]	Add-on to dipeptidyl peptidase-4 inhibitor (sitagliptin) with or without metformin; dapagliflozin (10mg) versus placebo	Trial yet to be published and there are limited details on study design	Greater reduction in HbA_{1c} at 24 weeks seen with dapagliflozin treatment compared with placebo in dual and triple therapy; results maintained at week 48	Significant HbA_{1c} reduction seen for triple therapy compared with placebo Only trial that looks at use with DPP-4 inhibitor, so shows this combination could have potential if sulphonylurea cannot be used This is not a common drug combination used in the UK and is not recommended by current NICE guidance
Wilding *et al*[7]	Add-on to insulin ≥30 units ± up to two oral antidiabetics; dapagliflozin (2.5mg, 5mg or 10mg) versus placebo	Insulin doses not titrated to target, although this was to enable interpretation of the effect of dapagliflozin No details given of the original oral antidiabetic therapy Most patients enrolled were Caucasian and effects may vary in other ethnic groups	HbA_{1c} reduction was statistically higher for all doses compared with placebo; these were sustained to week 104	Demonstrated statistically significant benefit over placebo Higher rates of hypoglycaemia in comparison with placebo demonstrating a possible need for insulin dose reduction
Bolinder *et al*[8]	Body composition measurement; dapagliflozin (10mg) versus placebo in patients inadequately controlled on metformin	Significant differences between male and female populations studied Patients with body weight over 120kg were excluded which means those with the highest BMI cannot be included in the conclusions The study did not determine precise mechanism of dapagliflozin weight loss, and its effects on food intake and satiety are unknown	Mean weight loss of 2kg above placebo; proportion of patients achieving weight reduction of at least 5% was 26.2%	Greater effect seen in men than women; weight loss was mainly accounted for by fat loss rather than water Although this does not indicate significant benefits over other therapies (eg, glucagon-like peptide-1 agonists) it does offer weight loss benefits at an earlier stage in therapy and without the restrictions placed on GLP-1 agonists

DAPAGLIFLOZIN

SPECIAL GROUPS

RENAL IMPAIRMENT

- **DAPAGLIFLOZIN REQUIRES A GOOD LEVEL OF RENAL FUNCTION TO WORK**
- **EFFICACY IS REDUCED IN PATIENTS WHO HAVE MODERATE RENAL IMPAIRMENT AND IS PROBABLY ABSENT IN PATIENTS WITH SEVERE RENAL IMPAIRMENT**
- **IT IS NOT LICENSED FOR USE IN PATIENTS WITH A CREATININE CLEARANCE BELOW 60ml/mins**
- **HOWEVER NO DOSE ADJUSTMENT IS NEEDED FOR PATIENTS WITH MILD RENAL IMPAIREMENT**

DAPAGLIFLOZIN

SPECIAL GROUPS

HEPATIC IMPAIRMENT – DOSE ADJUSTMENT UNNECESSARY EXCEPT THOSE WITH SEVERE IMPAIRMENT (WHERE A STARTING DOSE OF 5mg IS RECOMMENDED)

OLD AGE – NO DOSE ADJUSTMENT BASED ON AGE. DUE TO LACK OF EXPOSURE IN PATIENTS ≥ 65 YRS, DAPAGLIFLOZIN IS NOT CURRENTLY RECOMMENDED IN THIS AGE GROUP.

DAPAGLIFLOZIN

SIDE EFFECTS

- URINARY AND GENITAL TRACT INFECTIONS
  - COMMON FINDING IN CLINICAL TRIALS
  - INCIDENCE OF GTI DOSE RELATED
  - INFECTIONS APPEAR TO BE MILD AND RESPONDED TO STANDARD THERAPY
- HYPOGLYCAEMIA
  - INCIDENCE WAS LOW BUT INCREASED WITH CONCURRENT SULPHONYLUREA OR INSULIN

DAPAGLIFLOZIN

SIDE EFFECTS

- **MALIGNANCY**
  - **AN ANALYSIS OF THE ADVERSE EFFECTS THAT OCCURED DURING CLINICAL TRIALS SUGGESTED THAT THERE WAS AN IMBALANCE IN THE OCCURENCE OF BOTH BLADDER CANCER (10 CASES) AND BREAST CANCER (9 CASES)**
  - **THE TRIALS WERE NOT OF ADEQUATE DESIGN, SIZE OR SCOPE TO DETECT A SIGNIFICANT RISK DIFFERENCE BETWEEN DAPAGLIFLOZIN AND COMPARATORS FOR THESE TYPES OF CANCER**
  - **HOWEVER THE FDA DETERMINED THAT THE NUMBER OF OBSERVED BREAST AND BLADDER CANCERS IN THE DAPAGLIFLOZIN TREATED GROUP EXCEEDED THE NUMBER OF CASES IN THE GENERAL DIABETIC POPULATION**

DAPAGLIFLOZIN

SIDE EFFECTS

- **HEPATIC IMPAIRMENT**
  - **THERE WERE AT LEAST 8 CASES OF DERANGED LIVER FUNCTION DURING THE PHASE 3 TRIALS WHICH INCLUDED RAISED SERUM ALANINE TRANSMINASE AND BILRUBIN TEST RESULTS. ONLY ONE CASE WAS THOUGHT TO BE RELATED TO DAPAGLIFLOZIN.**

DAPAGLIFLOZIN

INTERACTIONS

- FEW INTERACTIONS REPORTED DURING THE PHARMACOKINETIC STUDIES CARRIED OUT

- LACK OF EFFECT ON CYTOCHROME P450 $\longrightarrow$ INTERACTIONS ARE NOT EXPECTED WITH DRUGS METABOLISED BY THESE ENZYMES

- PATIENTS TREATED WITH MEDICINES THAT AFFECT RENAL FUNCTION SUCH AS ACE INHIBITORS/LOOP DURETICS SHOULD BE STARTED ON DAPAGLIFLOZIN CAUTIOUSLY

DAPAGLIFLOZIN

MARKETING AUTHORISATION

- IT HAS BEEN GRANTED EUROPEAN MARKETING AUTHORISATION (EMEA)
- IT WAS NOT RECOMMENDED FOR APPROVAL BY FDA BECAUSE OF CONCERNS OVER ITS ADVERSE EFFECTS PROFILE. FURTHER CLINICAL DATA HAVE BEEN REQUESTED BY THE FDA TO ALLOW BETTER ASSESSMENT OF RISKS
- THE EUROPEAN MEDICINES AGENCY'S COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE, HOWEVER BELIEVES THAT THE COMMONLY SEEN SIDE EFFECTS ARE MANAGEABLE
- IT HAS RECOMMENDED THOUGH THAT FURTHER STUDIES INVESTIGATING THE POTENTIAL CANCER RISKS BE CARRIED OUT
- THE MANUFACTURER PLANS TO CONDUCT POST-MARKETING TRIALS TO EVALUATE THE SAFETY PROFILE

DAPAGLIFLOZIN

PLACE IN THERAPY

- DAPAGLIFLOZIN WILL PROBABLY BE A THIRD LINE THERAPY OPTION FOR DIABETES, ALONGSIDE DPP4 INHIBITORS AND GLP-I AGONISTS
- HOWEVER WITH THE GROWING CONCERN REGARDING THE HYPOGLYCAEMIA RISK OF SULPHONYLUREAS, IT WILL PROBABLY BE PROMOTED TO BE USED EARLIER IN THE COURSE OF DIABETES AS AN ALTERNATIVE FOR PATIENTS IN WHOM SULPHONYLUREAS ARE CONTRAINDICATED
- FURTHERMORE THE WEIGHT LOSS SEEN DURING TRIALS WOULD BE AN ADDED BENEFIT
- AT THE MOMENT, DAPAGLIFLOZIN DOES NOT HAVE THE STRENGTH OF EVIDENCE TO SUPPORT IT REPLACING METFORMIN OR SULPHONYLUREAS AS FIRST AND SECOND LINE OPTIONS

DAPAGLIFLOZIN

PLACE IN THERAPY

- NONETHELESS, ITS NEW MODE OF ACTION ALLOW PRESCRIBERS ANOTHER OPTION TO TAILOR THERAPY TO MEET INDIVIDUAL NEEDS
- IT ALSO PRESENTS AN OPPORTUNITY TO PRESCRIBE WITH INSULIN DUE TO ITS INSULIN-DEPENDENT MECHANISM AND INSULIN SPARING EFFECTS

NICE GUIDANCE

- IS RECOMMENDED IN COMBINATION WITH METFORMIN AS AN OPTION FOR TYPE 2 DIABETES
- ALSO RECOMMENDS DAPAGLIFLOZIN IN COMBINATION WITH INSULIN FOR TREATING TYPE 2 DIABETES
- TRIPLE THERAPY REGIMEN IN COMBINATION WITH METFORMIN AND SULPHONYLUREA IS NOT RECOMMENDED
- ANOTHER DRUG IN THIS CLASS – *CANAGLIFLOZIN* - RECENTLY INTRODUCED

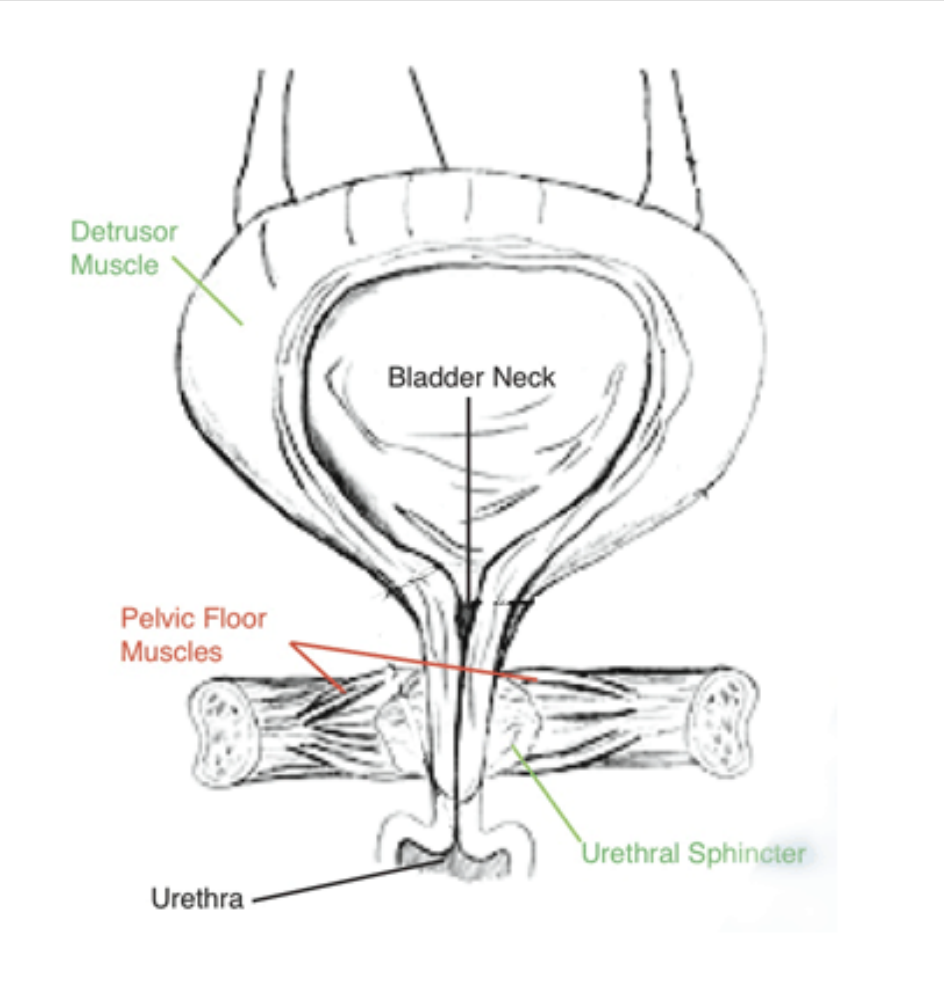
MANAGEMENT OF URINARY INCONTINENCE

MIRABEGRON A NEW DRUG FOR OVERACTIVE BLADDER

TYPES OF URINARY INCONTINENCE

- STRESS INCONTINENCE
- URGE INCONTINENCE
- OVERFLOW INCONTINENCE
- MIXED INCONTINENCE (A COMBINATION OF URGE/STRESS INCONTINENCE)
- OTHER FORMS (E.G NOCTURNAL ENURESIS)

THE BLADDER MECHANISM



STRESS INCONTINENCE

- CAUSED BY AN INCOMPETENT URETHRAL SPHINCTER THAT ALLOWS LEAKAGE OF URINE WHEN PRESSURE IS RAISED IN BLADDER SUDDENLY (E.G EXERCISING, LIFTING, COUGHING, ETC)

- CAUSES OF URETHRAL SPHINCTER INCOMPETENCE INCLUDE DIRECT DAMAGE TO THE PELVIC FLOOR MUSCLES (OFTEN ASSOCIATED WITH CHILDBIRTH), POST MENOPAUSAL OESTROGEN DEFICIENCY AND IN MEN PROSTATECTOMY OPERATIONS

- AGGRAVATED BY WEAK PELVIC FLOOR MUSCLES, OBESITY, CHRONIC COUGHS, ALPHA BLOCKING DRUGS (WHICH RELAX THE URETHRAL SPHINCTER), PREMENSTRUAL HORMONE FLUCTUATIONS AND EXERCISE

URGE INCONTINENCE

- CAUSED BY OVERACTIVITY OF THE DETRUSOR MUSCLE (BLADDER WALL)
- MANIFESTED AS URINARY URGENCY AND/OR FREQUENCY WITH OR WITHOUT INCONTINENCE, AND AS NOCTURIA
- DETRUSOR HYPERACTIVITY MAY BE IDIOPATHIC BUT IT MAY HAVE A NEUROPATHIC ORIGIN SUCH AS BRAIN INJURY OR CEREBROVASCULAR ACCIDENT
- CAN BE AGGRAVATED BY ANXIETY, ALCOHOL, ETC

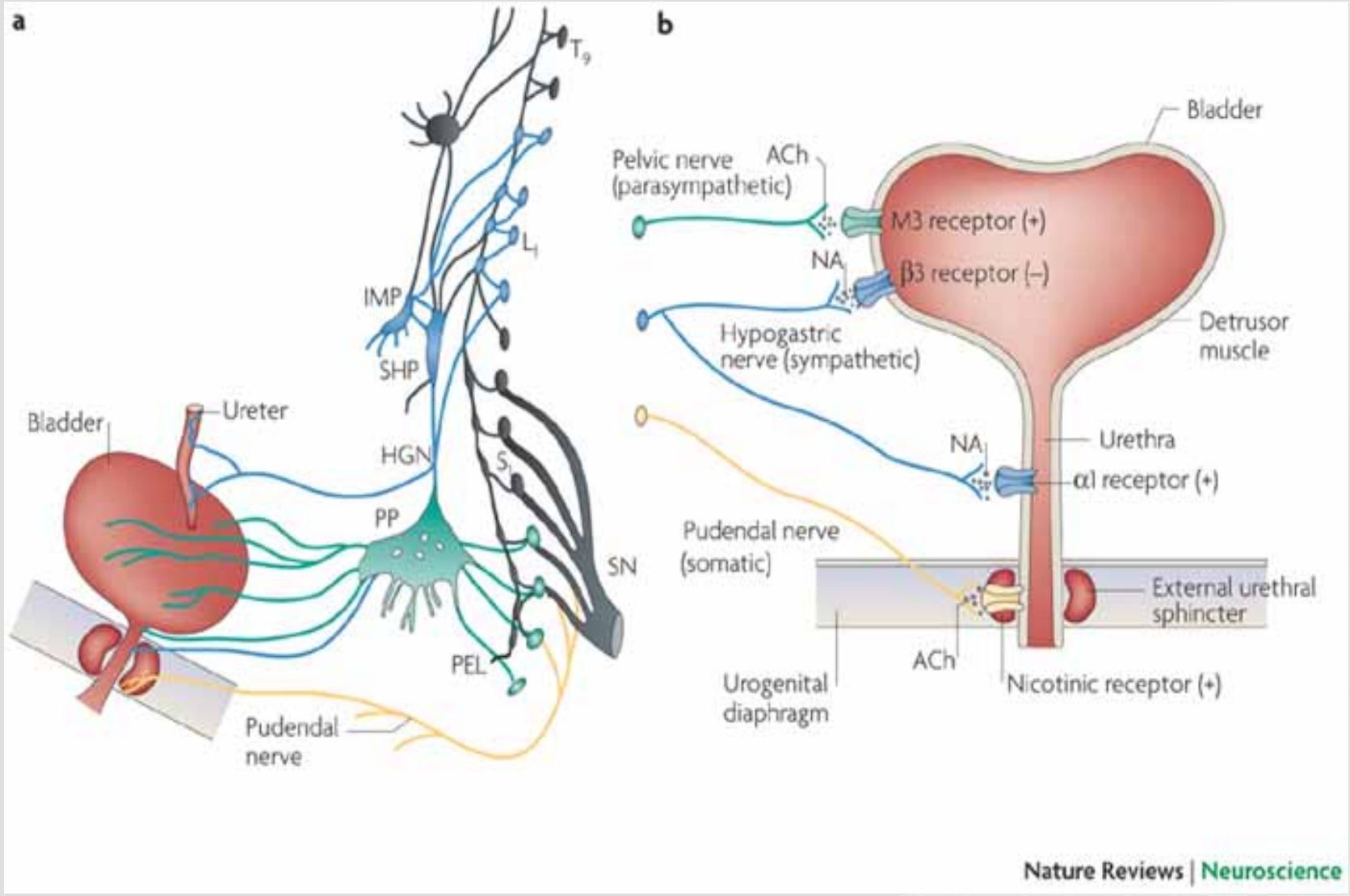
OVERFLOW INCONTINENCE

- PATIENT WILL PROBABLY HAVE NOCTURIA AND REPORT PASSIVE DRIBBLING OF URINE, FREQUENCY, INCOMPLETE BLADDER EMPTYING

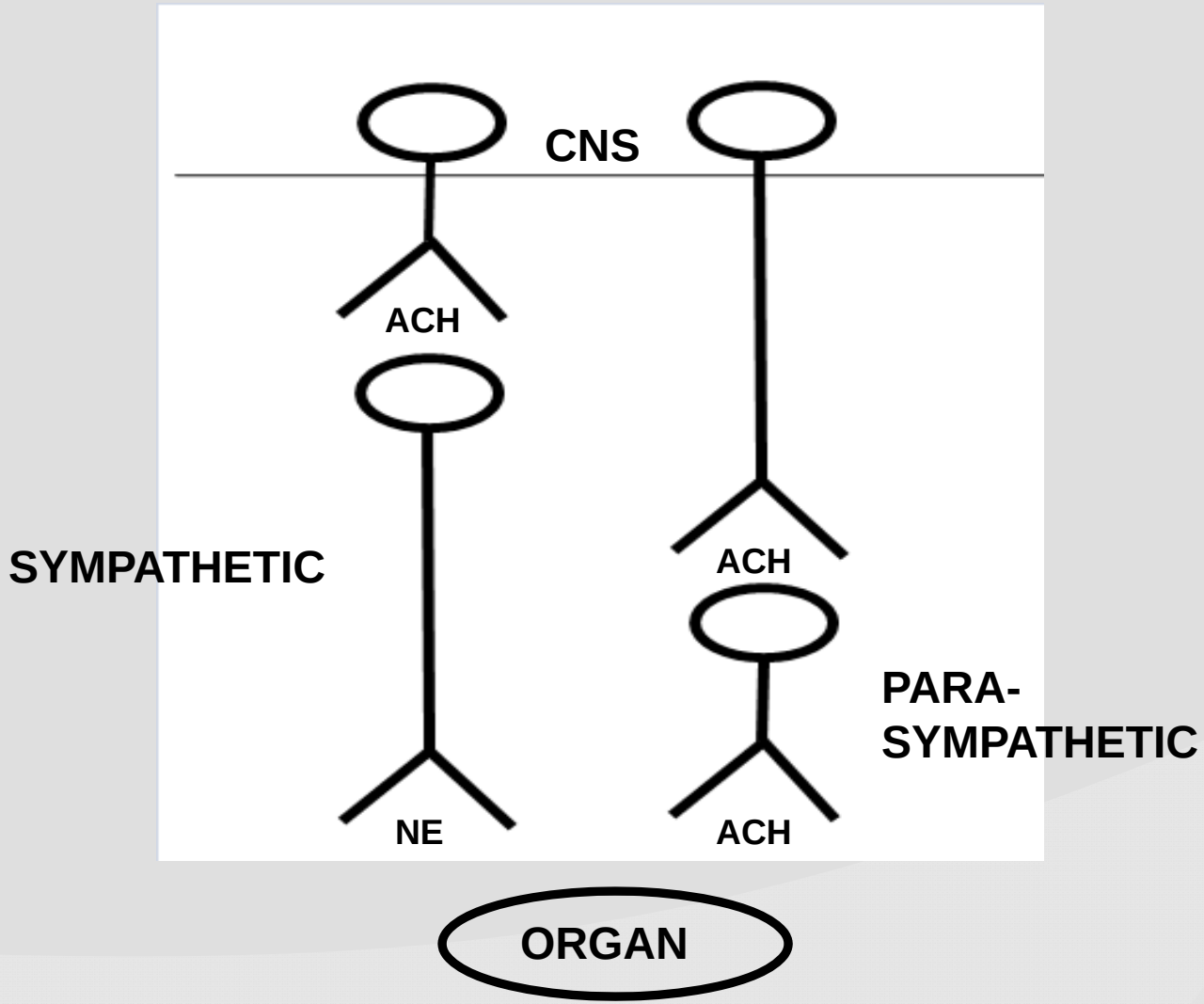
- A COMMON CAUSE IS OUTFLOW OBSTRUCTION DUE TO BENIGN PROSTATIC HYPERTROPHY (BPH) OR CANCER OF THE PROSTATE

PHARMACOLOGICAL CAUSES

- ANY INCONTINENT PATIENT SHOULD HAVE THEIR MEDICATION REVIEWED TO CHECK WHETHER SIDE EFFECTS OF DRUGS ARE A CONTRIBUTING FACTOR TO THEIR PROBLEM
- THESE INCLUDE FOR EXAMPLE ALPHA BLOCKERS, DIURETICS
- CAFFEINE MAY AGGRAVATE DETRUSOR OVERACTIVITY AND ALCOHOL CAN CAUSE DIURESIS, BOTH LEADING TO URGE INCONTINENCE


a
T9
L1
IMP
SHP
HGN
S1
PP
SN
PEL
Bladder
Ureter
Pudendal nerve
b
Bladder
Pelvic nerve (parasympathetic)
ACh
M3 receptor (+)
NA
β3 receptor (–)
Hypogastric nerve (sympathetic)
Detrusor muscle
NA
Urethra
α1 receptor (+)
Pudendal nerve (somatic)
External urethral sphincter
ACh
Nicotinic receptor (+)
Urogenital diaphragm
Nature Reviews | Neuroscience

DUAL INNERVATION OF URINARY BLADDER



MANAGEMENT OF URGE INCONTINENCE

- DECREASING CAFFEINE AND ALCOHOL INTAKE
- PELVIC FLOOR EXERCISES
- BLADDER RETAINING (PATIENTS ENCOURAGED TO KEEP A BLADDER RECORD CHART WHICH RECORDS WHEN URINE IS PASSED NORMALLY AND ANY LEAKAGE) – AIM IS TO INCREASE TIME BETWEEN VISITS OR VOLUME PASSED EACH TIME
- DRUG THERAPY: MOST EFFECTIVE DRUGS ARE ANTICHOLINERGICS WHICH RELAXES DETRUSOR MUSCLES
- OPTIONS INCLUDE: OXYBUTYNIN, TOLTERODINE, SOLIFENACIN AND TROSPIUM
- MANY PATIENTS BENEFIT WITH A LOW DOSE, TO FACILITATE TOLERANCE AND GRADUALLY INCREASING UNTIL MAXIMUM EFFECT IS ACHIEVED
- SIDE EFFECTS INCLUDE RETENTION, DRY MOUTH, CONSTIPATION, ETC
- NEWER DRUGS SUCH AS TOLTERODINE, TROSPIUM, SOLIFENACIN ARE MORE SPECIFIC FOR THE BLADDER. HENCE LESS SYSTEMIC SIDE EFFECTS

MANAGEMENT OF OVERFLOW INCONTINENCE (OUTFLOW OBSTRUCTION)

- **ENLARGED PROSTATE (BPH) CAN BE TREATED BY DRUGS**

  1. **ALPHA BLOCKERS (ALFUZOSIN), TAMSULOSIN, ETC)**
  2. **5-ALPHA REDUCTASE INHIBITORS (FINASTERIDE, DUTASTERIDE)**

- **SURGERY**

MANAGEMENT OF STRESS INCONTINENCE

- PELVIC FLOOR EXERCISES (FOR WOMEN AND FOR MEN POST-PROSTATECTOMY)
- ELECTROTHERAPY ADMINISTERED BY A COMPETENT CONTINENCE NURSE
- SURGERY
- DRUG THERAPY
  1. ORAL OR TOPICAL OESTROGEN REPLACEMENT IN POST MENOPAUSAL WOMEN
  2. DULOXETINE – NOVEL AND FIRST AGENT IN THE MANAGEMENT OF URINARY STRESS INCONTINENCE

DULOXETINE

- SEROTONIN AND NORADRENALINE REUPTAKE INHIBITOR BLOCKING THE UPTAKE OF THESE NEUROTRANSMITTERS IN THE SPINAL CORD
- THIS INCREASE IN THE NEUROTRANSMITTERS STIMULATES INCREASED ACTIVITY OF THE NERVE THAT STIMULATES THE URETHRAL SPHINCTER
- CONTRACTION OF THE SPHINCTER AT THE OPENING OF THE BLADDER, PREVENTING LEAKAGE OF THE URINE DUE TO PHYSICAL EXERTION

MIRABEGRON

A NEW DRUG FOR OVERACTIVE BLADDER (URGE INCONTINENCE)

"HOW IT WORKS"

- **MIRABEGRON IS THE FIRST B_3 ADENOCEPTOR AGONIST TO BE MARKETED**
- **IT'S LIKELY THAT MIRABEGRON EXERTS ITS EFFECTS VIA A DUAL MECHANISM BOTH DIRECTLY ON THE BLADDER SMOOTH MUSCLE AND ALSO VIA THE SENSORY NERVOUS SYSTEM**
- **BY STIMULATING B_3 RECEPTORS, IT INCREASES LEVEL OF CYCLIC AMP AND LEADS TO RELAXATION OF DETRUSOR MUSCLE**
- **MAIN ADVANTAGE IS LACK OF MUSCARINIC SIDE EFFECTS**

MIRABEGRON

EVIDENCE

MIRABEGRON APPEARS TO BE MORE EFFECTIVE THAN PLACEBO IN TRIALS IN TERMS OF REDUCTION OF INCONTINENCE EPISODES AND MICTURITIONS BUT THE DIFFERENCE IS NOT STATISTICALLY SIGNIFICANT COMPARED TO TOLTERODINE

MIRABEGRON

ADMINISTRATION

- ONCE DAILY WITH OR WITHOUT FOOD
- 50mg DAILY RECOMMENDED FOR MOST ADULT PATIENTS

SIDE EFFECTS (IN TRIALS)

- URINARY TRACT INFECTION (5.9%)
- HEADACHE (4%)

MIRABEGRON

MARKETING AUTHORISATION

- AVAILABLE IN JAPAN AND US FOR OVER A YEAR
- RECENTLY REGISTERED IN UK
- SO FAR, IT APPEARS TO HAVE VERY FEW SIDE EFFECTS
- PRACTICALLY NO ANTIMUSCARINIC SIDE EFFECTS
- THE SUMMARY OF PRODUCT CHARACTERISTICS LISTS URINARY TRACT INFECTIONS AND TACHYCARDIA AS THE MOST COMMON SIDE EFFECTS (THE LATTER AFFECTING 1.2% OF PATIENTS)

MIRABEGRON

PLACE IN THERAPY

- IT IS LIKELY THAT MIRABEGRON WILL START AS AN ALTERNATIVE TO PATIENTS WHO FAIL OR CANNOT TOLERATE ANTIMUSCARINIC TREATMENT

- WITH MORE EXPERIENCE OF ITS USE, IT COULD BE USED FIRST LINE BUT IT IS NOT A CANDIDATE YET

- IT MIGHT ALSO BE USED IN THE FUTURE IN COMBINATION WITH ANTIMUSCARINIC (BUT FURTHER STUDIES AWAITED)

MIRABEGRON

NICE RECOMMENDS MIRABEGRON AS A POSSIBLE TREATMENT FOR SYMPTOMS OF OVERACTIVE BLADDER IN SOME PEOPLE FOR WHOM THE "ANTIMUSCARINIC DRUGS" DO NOT WORK, ARE NOT SUITABLE FOR, OR HAVE UNACCEPTABLE SIDE EFFECTS.

(TYPICALLY 30% OF PATIENTS CANNOT TOLERATE THE SIDE EFFECTS OF ANTIMUSCARINIC DRUGS OR FIND TREATMENT TO BE INEFFECTIVE)

COSMECEUTICALS/DERMACEUTICALS

A NEW CLASS OF PRODUCTS IN DERMATOLOGY

WHAT IS A COSMECEUTICAL?

A TERM COINED FROM

- ***COSMETIC*** **- A PRODUCT MEANT TO BEAUTIFY OR IMPROVE APPEARANCE**

AND

- ***DRUG*** **– A PRODUCT MEANT TO TREAT, MITIGATE OR PREVENT DISEASE**

COSMECEUTICAL

DEFINITION

- COSMECEUTICALS REFERS TO THE COMBINATION OF COSMETICS AND PHARMACEUTICALS
- COSMECEUTICALS ARE COSMETIC PRODUCTS WITH BIOLOGICALLY ACTIVE INGREDIENTS PURPORTING TO HAVE MEDICAL OR DRUG-LIKE BENEFITS
- ALSO REFERRED TO AS DERMACEUTICALS
- APPLIES ONLY TO PRODUCTS APPLIED TOPICALLY SUCH AS CREAMS, LOTIONS, OINTMENT, ETC
- DOES NOT UNDERGO RIGOROUS TESTING AS IT IS THE CASE FOR PHARMACEUTICALS AND IS NOT REGULATED
- FASTEST GROWING SEGMENT OF THE COSMETICS AND PERSONAL CARE INDUSTRY

COSMETIC SKIN DISORDERS

COMMON COSMETIC SKIN ORDERS

- **AGING SKIN**
- **PHOTO AGING**
- **SMOKING RELATED SKIN DISORDERS**
- **DRY SKIN**
- **PIGMENT DISORDERS**
- **SCARRING**
- **HAIR GROWTH DISORDERS**
- **TELANGIECTASIA**

COSMECEUTICALS

PRODUCT LINES:

- **ANTI-AGING THERAPY (ACCOUNTS FOR 95% OF COSMECEUTICAL BUSINESS)**
- **SUN PROTECTION**
- **ANTI-ACNE**
- **DEPIGMENTING AGENTS**
- **MOSTURISERS**

-ANTI-AGING THERAPY HAS A DOUBLE DIGIT GROWTH IN MOST GLOBAL MARKET

-GLOBAL COSMECEUTICAL MARKET IS ESTIMATED AT $ 30 BILLION

-EMERGING SEGMENTS ARE:

- **HAIR**
- **TOOTH WHITENING**
- **LIP PROTECTION**

COSMECEUTICAL

3 ESSENTIAL QUESTIONS

- **DOES IT PENETRATE?**
- **DO WE KNOW HOW IT WORKS?**
- **DOES IT SHOW CLINICAL SIGNIFICANCE?**

Some Cosmeceuticals

Gau et. Al. (2008) Clinics in Dermatology 26 367-374

Table 1 Examples of some cosmeceutical ingredients (in alphabetical order)

Ingredients	Purported action	Source
AHAs	Exfoliation and improving circulation	Fruit acids (glycolic acid, lactic acid, citric acid, titanic acid, pyruvic acid, maleic acid, etc)
Allantoin	Soothing the skin	Comfrey root
Aloe vera power	Softening the skin	Aloe vera
α-Lipoic acid	Free radical scavengers and antioxidant	Plants and animals
Arjunolic extract	Antioxidant and anti-inflammation	*Terminalia arjuna*
β-Bisabolol	Anti-inflammation, antibacteria	Chamomile flower
β-Hydroxy acids	Antibacteria	Plants
Boswellic acids	Anti-inflammation and antiaging	*Boswellia serrata*
Calendula oil	Soothing, softening, and cell renewal	*Calendula officinalis*
Centella extracts	Skin conditioning, increasing collagen production, improving texture and integrity of skin	*Centella asiatica*
Coenzyme Q10 (ubiquinone)	Cellular antioxidants	Naturally occurring in skin
Coleus forskohlii oil	Antimicrobial, aromatherapy/perfume	*C. forskohlii*
Coriander seed oil	Anti-inflammation, skin lightening	*Coriandrum sativa*
Dry extract from yarrow	Treatment of oily hair	*Achillea millefolium*
Essential fatty acids	Smoothening, moisturizing, and protection	Linoleic, linolenic, and arachidonic acids
Furfuryladenine	Improve hydration and texture of skin	Plant growth hormone
Ginkgo extracts	Antioxidants, smoothing, rejuvenation of skin	*Ginkgo biloba*
Green tea extract	Antiaging and antioxidants	Green tea
Horse chestnut extract	Supporting blood circulation, wound healing, and anti-inflammation	*Aesculus hippocastanum*
Kinetin	Free radical scavenger and antioxidant	Plants and yeast
Licorice extract	Skin whitening, antioxidant, antimicrobial, and anti-inflammation	*Glycyrrhiza glabra*
Lupeol	Antioxidant and skin conditioning	*Cratacva nurvula*
Neem oil limonoids	Antimicrobial	*Azadirachta indica*
Oleanolic extract	Antioxidant, improving texture and integrity of skin	Olive leaf
Panthenol	Moisturizing and soothing skin	Provitamin B_5
Pycnogenol	Antiaging	Grape seed
Retinoids	Smoothing, promoting cell renewal, and improving circulation of skin	β-Carotene derivatives or synthetic compounds with similar mechanisms of action
Rosemary extract	Antioxidants, anti-inflammation	*Rosemarinus officinalis*
Sodium hyaluronate	Lubricant, natural moisturizer	Natural protein
Tetrahydrocurcuminoides	Antioxidant and antiaging	*Curcuma longa*
Turmeric oil	Antibacterial and inflammation	*C. longa*
Ursolic acid	Anti-inflammatory, collagen building up	*R. officinalis*
Vitamins A, E, and C	Antioxidants	
Witch hazel	Tones	*Hamamelis virginiana*

COMMONLY USED SUBSTANCES IN COSMECEUTICAL FORMULATIONS

1. *MOSTURISING AGENTS*

- RESTORE WATER CONTENT TO THE EPIDERMIS
- PROVIDE A SOOTHING PROTECTIVE FILM
- THEY IMPROVE THE APPEARANCE AND TACTILE PROPERTIES OF DRY AND AGING SKIN, RESTORE THE NORMAL BARRIER FUNCTION OF THE SKIN AND REDUCE THE RELEASE OF INFLAMMATORY MEDIATORS
- MOISTURISERS COMPRISE AN IMPORTANT THERAPEUTIC COMPONENT IN THE MANAGEMENT OF VARIOUS SKIN CONDITIONS
- COMMON INGREDIENTS ARE LIQUID PARAFFIN , WHITE SOFT PARAFFIN, GLYCERINE, PETROLEUM JELLY, CERAMIDES, PENTYLENE GLYCOL

COMMONLY USED SUBSTANCES IN COSMECEUTICAL FORMULATIONS

2. *DEPIGMENTING AGENTS*

- **SKIN LIGHTENING AGENTS ADDED TO PRODUCT FORMULATIONS HAVE BECOME INCREASINGLY POPULAR**

- **COMMON INGREDIENTS INCLUDE HYDROQUINONE, ASCORBIC ACID (VITAMIN C), KOJIC ACID AND LICORICE EXTRACT**

HYDROQUINONE **- HAS BEEN AGENT OF CHOICE FOR SKIN LIGHTENING**

- CONCERNS OVER PERMANENT DEPIGMENTATION/CARCINOGENICITY

- BANNED IN MANY COUNTRIES

COMMONLY USED SUBSTANCES IN COSMECEUTICAL FORMULATIONS

3. ***EXFOLIANTS***
   - **PROMOTE SKIN TURNOVER BY REMOVING ADHERENT CELLS IN STRATEUM CORNEUM**
   - **COMMON EXFOLIANTS INCLUDE SALICYLIC ACID (SA), LACTIC ACID AND GLYCOLIC ACID**

4. ***SUN SCREENS***
   - **SUN SCREENS ARE THE SINGLE MOST IMPORTANT COSMECEUTICAL BECAUSE THEY PROTECT AGAINST SOLAR RADIATION, THE MOST IMPORTANT DAMAGING ENVIRONMENTAL AGENT**
   - **AS A RESULT, THEY HELP PREVENT THE SIGNS OF AGING**
   - **TO BE EFFECTIVE, SUN SCREENS SHOULD PROVIDE BROAD SPECTRUM COVERAGE THAT INCLUDES BOTH UVA/UVB BLOCKING AGENTS TO INHIBIT PHOTO AGING AND BE PART OF A DAILY SKIN CARE REGIMEN**

COMMONLY USED SUBSTANCES IN COSMECEUTICAL FORMULATIONS

5. ***ANTIOXIDANTS***

- **REDUCE FREE RADICAL DAMAGE THEREBY PREVENTING IMPAIRMENT AT CELLULAR LEVEL**

- **THEY INHIBIT INFLAMMATION, WHICH LEADS TO A COLLAGEN DEPLETION, AND THEY OFFER PROTECTION AGAINST PHOTO DAMAGE AND SKIN CANCER**

- **COMMON INGREDIENTS INCLUDE:**

  ALPHA LIPOIC ACID

  VITAMIN C

  NIACINAMIDE (VITAMIN B3)

  N-ACETYL GLUCOSAMINE

  UBIQUINONE

COMMONLY USED SUBSTANCES IN COSMECEUTICAL FORMULATIONS

6. *RETINOIDS*

- **AMONG THE MOST COMMON INGREDIENTS FOUND IN COSMECEUTICAL AGENTS**
- **THE MOST STUDIED AND THE MOST DATA BEHIND THEM**
- **CONSIST OF NATURAL AND SYNTHETIC DERIVATIVES OF VITAMIN A THAT REDUCE HYPER PIGMENTATION AND INHIBIT ENZYMES FROM BREAKING DOWN COLLAGEN**
- **MANY OF THEIR COSMECEUTICAL CLAIMS ARE BASED ON DATA DERIVED FROM STUDIES ON TRETINOIN AND OTHER CLASSES OF RETINOID DRUGS**

COMMONLY USED SUBSTANCES IN COSMECEUTICAL FORMULATIONS

6. *RETINOIDS* (CONTINUED)

- SOME KEY RETINOIDS INCLUDE RETINOIC ACID (TRETINOIN), RETINOL, RETINALDEHYDE
- EXTENSIVE LITERATURE ON THE USE OF TRETINOIN, WHICH IS CONSIDERED ONE OF THE MOST POTENT AGENTS FOR TREATING THE SIGNS OF AGING AND/OR PHOTO DAMAGED SKIN INCLUDING FINE LINES, HYPER PIGMENTED SPOTS AND WRINKLES
- HOWEVER SIDE EFFECTS SUCH AS BURNING AND SCALING HAVE LIMITED ITS ACCEPTANCE. IN ORDER TO MINIMIZE THESE SIDE EFFECTS, VARIOUS NOVEL DRUG DELIVERY SYSTEMS ARE BEING DEVELOPED
- RETINOL IS OXIDISED INTO RETINALDEHYDE AND THEN INTO RETINOIC (TRETINOIN), THE BIOLOGICALLY ACTIVE FORM OF VITAMIN A. MODEST ACTIVITY COMPARED TO RETINOIC ACID (TRETINOIN)

COMMONLY USED SUBSTANCES IN COSMECEUTICAL FORMULATIONS

7. *BOTANICALS*

- **LARGEST GROUP OF COSMECEUTICALS FOUND IN MARKET PLACE TODAY**
- **THEIR USE IS UNREGULATED AND OFTEN UNSUPPORTED BY SCIENCE**
- **SOME BOTANICALS THAT MAY BENEFIT THE SKIN INCLUDE: GREEN TREE EXTRACT, GRAPE SEED EXTRACT AND FERULIC ACID**

COMMONLY USED SUBSTANCES IN COSMECEUTICAL FORMULATIONS

8. *(i) Topical Peptides*

- ARE REGARDED AS CELLULAR MESSENGERS THAT ARE FORMED FROM AMINO ACIDS AND ARE DESIGNED TO MIMIC PEPTIDE FRAGMENTS WITH ENDOGENOUS BIOLOGIC ACTIVITY.

- PLAY A ROLE IN SIGNALLING FIBROBLASTS TO PROVIDE COLLAGEN IN THE SKIN WHICH CAN IMPROVE THE APPEARANCE OF SKIN

(II) GROWTH FACTORS

- COMPRISE A LARGE GROUP OF REGULATORY PROTEINS THAT ATTACH TO CELL SURFACE RECEPTORS TO MEDIATE INTER AND INTRACELLULAR SIGNALLING PATHWAYS

- GROWTH FACTORS RELEVANT TO WOUND HEALING MAY INDUCE NEW COLLAGEN, ELASTIN FORMATION AND MEDIATE ANGIOGENESIS. ONE HUMAN GROWTH FACTOR BEING USED PRESENTLY IS GROWTH FACTOR B, WHICH IS DERIVED FROM CULTURED FIBROBLASTS HARVESTED FROM NEONATAL FORESKIN.

COMMONLY USED SUBSTANCES IN COSMECEUTICAL FORMULATIONS

(II) GROWTH FACTORS

- **ADVANCES IN BIOTECHNOLOGY HAVE LEAD LO FURTHER PRODUCTS SUCH AS PROCESSED SKIN CELL PROTEINS HARVESTED FROM FETAL CELL LINES**

- **OTHER GROWTH FACTORS INCLUDE PLACENTAL EXTRACT, PLATELET DERIVED GROWTH FACTOR, RECOMBINANT EPIDERMAL GROWTH FACTOR**

COMMONLY USED SUBSTANCES IN COSMECEUTICAL FORMULATIONS

9. *ALPHA HYDROXY ACIDS (AHA)*

- **ALSO REFERRED TO AS FRUIT ACIDS**
- ***EXAMPLES:*** **CITRIC ACID, LACTIC ACID, GLYCOLIC ACID, MALIC ACID, PYRUVIC ACID, TARTARIC ACID**
- **IMPROVES SKIN TEXTURE AND REDUCE THE SIGNS OF AGING BY PROMOTING CELL SHEDDING IN THE OUTER LAYERS OF THE EPIDERMIS AND BY RESTORING HYDRATION.**

COSMECEUTICALS

IMPORTANCE OF VEHICLES

ONE OF THE MOST IMPORTANT PARTS IS THE VEHICLE THAT CARRIES THE ACTIVE INGREDIENT INTO THE SKIN.

VEHICLE DELIVERY SYSTEM CAN:

- **AUGMENT THE EFFICACY OF THE ACTIVE INGREDIENT**
- **INACTIVATE OR DIMINISH THE EFFICACY OF THE ACTIVE INGREDIENT**
- **IMPROVE THE SKIN BARRIER**
- **PROVOKE ALLERGIC CONTACT DERMATITIS ⟶ LOOK FOR A HYPOALLERGENIC FORMULATION , DERMATOLOGICALLY TESTED**

MOST FREQUENT ALLERGENS IN COSMETICS

ALLERGENS

- **NICKEL SULPHATE**
- **PERFUME-MIX**
- **P-PHENYLENDIAMIN**
- **LANOLIN (WOOLWAX)**
- **KALIUM DICHROMATE**
- **PARABENS**
- **EPOXID RESIN**
- **FORMALDEHYDE DONATOR**
- **THIURAM-MIX**
- **METHYL DIBROMOGLUTARONITRIL/PHENOXYETHANOL**
  (MDBGN) (PE)
- **METHYL CHLORISOTNIAZOLINON/METHYLSOTHIAZOLINON**
  (MCI) (MI)

TYPICAL ALLERGENS IN COSMETICS: SUCH AS
PERFUMES/PRESERVATIVES

➡ ***ONLY AVOIDING HELPS!***

TELAVANCIN – THE FIRST OF AN INNOVATIVE CLASS OF ANTIBIOTICS FOR THE MANAGEMENT OF HOSPITAL ACQUIRED PNEUMONIA

TELAVANCIN

- NEW CLASS OF ANTIBIOTIC (LIPOGLYCOPEPTIDE)
- INDICATED FOR THE TREATMENT OF ADULTS WITH HOSPITAL ACQUIRED PNEUMONIA (INCLUDING VENTILATOR ASSOCIATED PNEUMONIA), CAUSED BY METHICILLIN RESISTANT STAPHYLOCOCUS AUREUS (MRSA) WHERE OTHER TREATMENTS ARE NOT SUITABLE
- OFFERS A DUAL MECHANISM OF ACTION (IN A SIMILAR WAY TO VANCOMYCIN) – BINDS TO AND PREVENT POLYMERISATION OF BACTERIAL CELL WALL CONSTITUENTS/INTERACTS WITH THE CELL MEMBRANE CAUSING DEPOLARISATION $\longrightarrow$ LEADING TO CELL DEATH

TELAVANCIN

- ADMINISTERED ONCE DAILY BY IV INFUSION AND, UNLIKE VANCOMYCIN, DOES NOT REQUIRE THERAPEUTIC DRUG MONITORING
- 60% OF STAPH AUREUS ARE METHICILIN RESISTANT AND MORTALITY RATES FOR HOSPITAL ACQUIRED PNEUMONIA RANGE FROM 30% TO 70%
- VANCOMYCIN, LINEZOLID AND TELCOPLANIN ARE THE OTHER ANTIBIOTICS TO TREAT HAP/VAP CAUSED BY MRSA AND OTHER SERIOUS GRAM POSITIVE BACTERIAL INFECTIONS

TELAVANCIN

- POOLED DATA FROM TWO RANDOMISED CONTROLLED TRIALS, INVOLVING MORE THAN 1500 PATIENTS SHOW THAT 7-21 DAYS OF INTRAVENOUS TELAVANCIN (10mg/kg/24 hours) PRODUCES SIMILAR CURE RATES TO IV VANCOMYCIN (1g every 12 hours) IN HOSPITALS ACQUIRED PNEUMONIA SUSPECTED TO BE CAUSED BY GRAM POSITIVE PATHOGENS. CURE RATES WITH TELAVANCIN WERE 58.9% AT 7-14 DAYS AFTER THE END OF TREATMENT AND 59.5% WITH VANCOMYCIN.

TELAVANCIN

MOST COMMON SIDE EFFECTS:

- **FUNGAL INFECTIONS**
- **INSOMNIA**
- **DISTURBANCE OF TASTE**
- **HEADACHE**
- **PRURITUS**
- **RASH**
- **FATIGUE**
- **GASTROINTESTINAL DISTURBANCES**
- **FOAMY URINE**
- **RAISED BLOOD LEVELS OF CREATININE/LIVER ENZYMES**
- **ACUTE RENAL FAILURE**

SUVOREXANT – A DUAL OREXIN RECEPTOR

ANTAGONIST FOR MANAGEMENT OF INSOMNIA

INSOMNIA

- CHARACTERISED SUBJECTIVELY
- CONSISTS OF A VARIETY OF COMPLAINTS INCLUDING DIFFICULTY FALLING ASLEEP, DIFFICULTY MAINTAINING SLEEP OR EXPERIENCING NON RESTORATIVE SLEEP
- DESPITE A NUMBER OF AVAILABLE TREATMENTS, INSOMNIA IS THE MOST COMMON MEDICAL COMPLAINT IN GENERAL PRACTICE
- IT AFFECTS 30% OF ADULT POPULATION
- IT IS ALSO A MAJOR RISK FACTOR FOR ANXIETY DISORDER, SUBSTANCE ABUSE, AND MAJOR DEPRESSION, AND IT MAY LEAD TO DECREASED QUALITY OF LIFE

DRUGS USED IN THE MANAGEMENT OF INSOMNIA

A. **BENZODIAZEPINES**

B. **THE Z-DRUGS: ZOLPIDEM, ZOPICLONE, ZALEPLON**

- **THEY ARE GABA ACTING HYPNOTICS**

OTHER LESS FREQUENTLY USED DRUGS

- **SEDATING ANTIDEPRESSANTS**
- **ANTIHISTAMINES**
- **MELATONIN**

DIMINISHED EFFICACITY AND NEGATIVE SIDE EFFECTS LIMIT THE USE OF THESE TREATMENT OPTIONS FOR MANY PATIENTS

SUVOREXANT – AN OREXIN RECEPTOR ANTAGONIST

- FIRST IN A NEW CLASS OF DRUGS
- PROMOTE THE NATURAL TRANSITION FROM WAKEFULNESS TO SLEEP BY INHIBITING THE WAKEFULNESS PROMOTING OREXIN NEURONS OF THE AROUSAL SYSTEM
- SUROVEXANT IMPROVES SLEEP ONSET AND SLEEP MAINTENANCE
- THIS UNIQUE ALTERNATIVE HAS A FAVORABLE TOLERABILITY AND LIMITED SIDE EFFECT PROFILE

SUVOREXANT

MECHANISM OF ACTION

- **POTENT DUAL OREXIN RECEPTOR ANTAGONIST THAT BLOCKS BOTH OX1R AND OX2R**
- **PROMOTES SLEEP THROUGH THE BINDING INHIBITION OF OREXIN A AND B NEUROPEPTIDES THAT PROMOTE WAKEFULNESS**
- **ROUGHLY 70,000 OREXIN NEURONS ARE IN THE HUMAN BRAIN, LOCATED IN THE PERIFORNICAL LATERAL HYPOTHALAMUS WHICH SEND SIGNALS THROUGHOUT THE BRAIN AND SPINAL CORD**

SUVOREXANT

PHARMACOKINETICS/PHARMACODYNAMICS

- **THE FDA APPROVAL INCLUDED 32 STUDIES THAT ENROLLED MORE THAN 900 SUBJECTS (HEALTHY/INSOMNIACS)**
- **SUVOREXANT WAS EFFECTIVE AND GENERALLY WELL TOLERATED**
- **MAIN ADVANTAGE OVER PREVIOUS INSOMNIA THERAPIES IS THE LOW POTENTIAL FOR ADDICTION/DEPENDENCE**

SUVOREXANT

PHARMACOKINETICS/PHARMACODYNAMICS

- ***ABSORPTION***
  - **ONSET OF SLEEP OCCURRED BETWEEN 56-68 MINUTES AFTER ORAL ADMINISTRATION**
  - **MEDIAN PEAK PLASMA CONCENTRATIONS OCCUR APPROXIMATELY 2 HOURS AFTER ADMINISTRATION AND ARE NOT AFFECTED BY FOOD**

- ***METABOLISM***
  - **AGENT IS PRIMARILY METABOLISED BY CYTOCHROME P450 (CYP3A4) ENZYME SYSTEM INTO AN INACTIVE METABOLITE**

- ***ELIMINATION***
  - **ELIMINATED AS INACTIVE METABOLITES IN THE FAECES; THERE IS NO RENAL ELIMINATION**

SUVOREXANT

- **INDICATION: TREATMENT OF INSOMNIA (DIFFICULTY OF SLEEP ONSET OR SLEEP MAINTENANCE) IN ADULTS 18 YEARS AND OLDER**
- **NO CONTRAINDICATIONS EXCEPT NARCOLEPSY**
- **ADVERSE EFFECTS**

Adverse Drug Events Associated With Suvorexant and Placebo

Adverse Events	Placebo	10 mg	20 mg	40 mg	80 mg
Somnolence	0.4%	1.6%	4.9%	10.2%	11.5%
Sedation	0.4%	0	0	0	3.3%
Muscle Weakness	0	0	0	3.4%	1.6%
Abnormal dreams	0.8%	1.6%	0	0	4.9%
Headache	2.4%	0	16%	5.1%	4.9%

From Herring WJ , et al Neurology 2012;79(23):2265-2274

- **ABRUPT DISCONTINUATION OF SUVOREXANT AFTER CHRONIC USE DOES NOT RESULT IN REBOUND INSOMNIA OR WITHDRAWAL EFFECTS**
- **SUVOREXANT HAS THE POTENTIAL TO PRODUCE DROWSINESS THE NEXT DAY THAT MIGHT INTERFERE WITH DAILY ACTIVITIES**

SUVOREXANT

DRUGS INTERACTIONS

- AVOID TAKING OTHER CYP3A MEDICATIONS WHILE TAKING SUVOREXANT
- POTENT CYP3A INHIBITORS SUCH AS FLUCONAZOLE INCREASE PLASMA CONCENTRATIONS, PLACING PATIENTS WELL ABOVE THE DESIRED THERAPEUTIC THRESHOLD
- CYP3A INDUCERS SUCH AS RIFAMPICIN RESULT IN SIGNIFICANTLY REDUCED SUVOREXANT PLASMA CONCENTRATIONS

DOSAGE

- INITIAL DOSE IS 10MG
- DOSE MAY BE TITRATED UP TO 20MG DAILY.
- ESCALATION IS ADVISED ONLY IN THOSE PATIENTS WHO CAN TOLERATE LOWER DOSES WITH NO ADVERSE EFFECTS.
- DOSE TAKEN WITHIN 30 MINUTES OF GOING TO BED WITH AT LEAST 7 HOURS REMAINING BEFORE THE PLANNED TIME OF AWAKENING

Comparison with over Insomnia medications

- BOTH BZPS AND Z-DRUGS EXERT EFFECTS ON GABA AND HAVE MORE GLOBAL INHIBITORY EFFECTS ON THE BRAIN
- THIS EFFECT RESULTS IN AMNESIA, NEXT DAY SEDATION AND REBOUND INSOMNIA
- BOTH DRUGS ARE HABIT-FORMING AND HAVE THE POTENTIAL TO PROMOTE DEPENDENCE
- FOR THESE REASONS, THESE AGENTS ARE USED INTERMITTENTLY OR FOR SHORT DURATION
- SUVOREXANT'S MECHANISM OF ACTION DIFFERS FROM THAT BZPS AND Z-DRUGS: IT HAS NO EFFECT ON GABA
- INSTEAD OF PROMOTING SLEEP, IT INACTIVATES WAKEFULNESS
- ADVERSE EFFECTS COMMONLY OBSERVED WITH BZPS AND Z-DRUGS ARE VIRTUALLY ELIMINATED
- AS A RESULT, SUVOREXANT CAN BE USED DAILY ON A LONGER TERM BASIS WITH MINIMAL RISK OF PHYSICAL DEPENDENCE AND REBOUND INSOMNIA
- ADVERSE EFFECTS SEEM TO BE MORE PRONOUNCED IN PATIENTS 65 YEARS AND OLDER

SUVOREXANT

CONCLUSION

- PATIENTS WHO EXPERIENCE BOTH SLEEP ONSET AND SLEEP MAINTENANCE INSOMNIA MAY BE PARTICULARLY CHALLENGING TO TREAT. SUVOREXANT IS A GOOD OPTION IN SUCH PATIENTS
- EVIDENCE SUGGESTS THAT SUVOREXANT OFFERS A SUSTAINED BENEFIT FOR PATIENTS WITH CHRONIC INSOMNIA
- MORE CLINICAL DATA AWAITED
- FDA APPROVAL IN AUGUST 2014

SOFOSBUVIR

- THE FIRST NON INTERFERON TREATMENT FOR HEPATITIS C
- NEW TREATMENT OPTION FOR CHRONIC HEPATITIS C WHICH OFFERS HOPE OF A CURE
- HAILED AS A MAJOR BREAKTHROUGH AND GAME CHANGER IN THE MANAGEMENT OF HEPATITIS C

SOFOSBUVIR

- EMEA/FDA APPROVAL IN 2014 (MARKETED AS SOLVADI)
- ORAL ADMINISTRATION
- MUST BE USED IN COMBINATION WITH RIBAVIRIN AND CAN BE USED WITH OR WITHOUT PEG INTERFERON ALFA. FOR PATIENTS WHO REQUIRE PEGINTERFERON, THE COMBINATION WITH SOFOSBUVIR MEANS A SHORTER DURATION OF TREATMENT FROM 24 WEEKS TO 12 WEEKS
- SOFOSBUVIR'S ACTIVE METABOLITE IS AN INHIBITOR OF HEPATITIS C VIRUS RNA POLYMERASE, WHICH IS ESSENTIAL FOR VIRAL REPLICATION IN HOST CELLS

SOFOSBUVIR

- HEPATITIS C IS CATEGORISED INTO SEVERAL VIRAL GENOTYPES, SUBTYPES AND STRAINS, WHICH MAY HAVE A DIFFERENT RESPONSE TO TREATMENT
- IN CLINICAL TRIALS WITH TREATMENT NAIVE PATIENTS, A SUSTAINED VIROLOGIC RESPONSE WAS REPORTED IN 90% OF PATIENTS WHO WERE GENOTYPE 1 OR 4 AND TREATED FOR 4 WEEKS
- SOFOSBUVIR WAS ALSO NON-INFERIOR IN A HEAD TO HEAD TRIAL WITH PEG INTERFERON ALFA, DURING WHICH 67% OF GENOTYPE 2 OR 3 PATIENTS HAD A SUSTAINED VIROLOGIC RESPONSE TO SOFOSBUVIR. THE RESPONSE WAS DIFFERENT AMONG GENOTYPE: 97% FOR TYPE 2 AND 56% FOR TYPE 3
- ACCORDING TO A PAPER IN THE NEW ENGLAND JOURNAL OF MEDICINE, HIGH RATES OF SUSTAINED VIROLOGIC RESPONSE WERE OBSERVED IN PATIENTS WHO HAVE TRADITIONALLY BEEN LESS LIKELY TO HAVE A SUSTAINED RESPONSE INCLUDING BLACK PATIENTS

SOFOSBUVIR

- WOMEN OF CHILD BEARING POTENTIAL RECEIVING TREATMENT AND MEN WITH FEMALE PARTNERS SHOULD USE EFFECTIVE CONTRACEPTION TO PREVENT PREGNANCY.

- NO SIDE EFFECTS HAVE BEEN IDENTIFIED THAT ARE SPECIFIC TO SOFOSBUVIR AND DURING COMBINATION TREATMENT THE SIDE EFFECTS WERE CONSISTENT WITH THOSE EXPECTED FOR RIBAVIRIN/PEGINTERFERON

- SHOULD NOT BE CO-ADMINISTERED WITH CARBAMAZEPINE, PHENYTOIN, RIFAMPICIN, ST JOHN'S WORT, ETC

ADVERSE EFFECTS

Regimen without Interferon-Alfa 24w vs. 12w vs. Placebo	Regimen with Interferon-Alfa SOF/PEG/RBV vs. Placebo
Fatigue 30% (38%) [24%]	Fatigue 30% [55%]
Headache 30% (24%) [20%]	Headache 36% [44%]
Nausea 13% (22%) [18%]	Nausea 34% [29%]
Insomnia 16% (15%) [4%]	Insomnia 25% [29%]
Pruritus 27% (11%) [8%]	Pruritus 17% [17%]
Anaemia 6% (10%) [0%]	Anaemia 21% [12%]
Asthenia 21% (6%)[3%]	Asthenia 5% [3%]
Chills 2% (2%) [1%]	Chills 17% [18%]
Influenza-like illness 6% (3%) [3%]	Influenza-like illness 16% [18%]

SOFOSBUVIR

DOSING 400MG DAILY (ONE TABLET) WITH CONCOMITANT RIBAVIRIN WITH OR WITHOUT PEG INTERFERON

COST: USD 33,000 FOR 28 TABLETS

MONITORING PARAMETERS

- ***EFFICACY MONITORING:***
  - **HCV-RNA AT BASELINE, DURING TREATMENT, AT THE END OF TREATMENT AND DURING FOLLOW-UP WHEN CLINICALLY INDICATED**

- ***TOXICITY MONITORING:***
  - **BILIRUBIN, LIVER ENZYMES AND SERUM CREATININE AT BASELINE AND PERIODICALLY WHEN CLINICALLY INDICATED**
  - **PRETREATMENT AND MONTHLY PREGNANCY TEST UP TO 6 MONTHS FOLLOWING THERAPY**

Summary of preliminary recommendations(NICE)

Population	Treatment History	Interferon Eligibility	Recommendation
Sofosbuvir in combination with peginterferon alfa and ribavirin			
Adults with genotype 1 HCV	treatment naive	interferon eligible	recommended
	treatment experienced	interferon eligible	recommended
Adults with genotype 3 HCV	treatment naive	interferon eligible	not recommended in people without cirrhosis recommended in people with cirrhosis
	treatment experienced	interferon eligible	recommended
Adults with genotype 4, 5, and 6 HCV	treatment naive	interferon eligible	not recommended
	treatment experienced	interferon eligible	not recommended
Sofosbuvir in combination with ribavirin			
Adults with genotype 1 HCV	treatment naive	interferon unsuitable	not recommended
	treatment experienced	interferon unsuitable	not recommended
Adults with genotype 2 HCV	treatment naive	interferon eligible	not recommended
	treatment naive	interferon unsuitable	recommended
	treatment experienced	interferon eligible	recommended
	treatment experienced	interferon unsuitable	recommended
Adults with genotype 3 HCV	treatment naive	interferon unsuitable	not recommended in people without cirrhosis recommended in people with cirrhosis
	treatment experienced	interferon unsuitable	not recommended in people without cirrhosis recommended in people with cirrhosis
Adults with genotype 4, 5, and 6 HCV	treatment naive	interferon unsuitable	not recommended
	treatment experienced	interferon unsuitable	not recommended

HCV – hepatitis C virus;

treatment naïve – people who have not had prior treatment for chronic hepatitis C;

treatment experienced – people who have had prior treatment with interferon based therapy for chronic hepatitis C which did not have an adequate response to that treatment

interferon unsuitable – includes people who are intolerant to and ineligible for interferon.

THANK YOU