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<< /K 30 /P 92 0 R /Pg 1617 0 R /S /P >>
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<< /K 31 /P 92 0 R /Pg 1617 0 R /S /H2 >>
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<< /K 32 /P 92 0 R /Pg 1617 0 R /S /P >>
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<< /K 15 /P 1585 0 R /Pg 1 0 R /S /P >>
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<< /K 17 /P 1585 0 R /Pg 1 0 R /S /P >>
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<< /K 21 /P 1585 0 R /Pg 1 0 R /S /P >>
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<< /K 24 /P 1587 0 R /Pg 1 0 R /S /P >>
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<< /K 59 /P 1596 0 R /Pg 1 0 R /S /P >>
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<< /K 36 /P 1569 0 R /Pg 3 0 R /S /P >>
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<< /K 63 /P 1575 0 R /Pg 3 0 R /S /P >>
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245 0 obj
<< /K 68 /P 1577 0 R /Pg 3 0 R /S /P >>
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<< /K 97 /P 92 0 R /Pg 3 0 R /S /P >>
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<< /K 98 /P 92 0 R /Pg 3 0 R /S /P >>
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<< /K [99 100] /P 1566 0 R /Pg 3 0 R /S /P >>
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<< /K 0 /P 92 0 R /Pg 13 0 R /S /P >>
endobj
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<< /K 1 /P 92 0 R /Pg 13 0 R /S /P >>
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<< /K 2 /P 92 0 R /Pg 13 0 R /S /P >>
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<< /K 3 /P 92 0 R /Pg 13 0 R /S /P >>
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<< /K 4 /P 92 0 R /Pg 13 0 R /S /P >>
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<< /K 5 /P 92 0 R /Pg 13 0 R /S /P >>
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<< /K 8 /P 92 0 R /Pg 13 0 R /S /P >>
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<< /K 10 /P 1553 0 R /Pg 13 0 R /S /P >>
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<< /K 37 /P 1561 0 R /Pg 13 0 R /S /P >>
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endobj

321 0 obj
<< /K 12 /P 92 0 R /Pg 15 0 R /S /P >>
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322 0 obj
<< /K 13 /P 92 0 R /Pg 15 0 R /S /H2 >>
endobj
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<< /K 21 /P 92 0 R /Pg 15 0 R /S /P >>
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<< /K 26 /P 92 0 R /Pg 15 0 R /S /P >>
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334 0 obj
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<< /K [31 << /MCID 0 /Pg 17 0 R /Type /MCR >>] /P 92 0 R /Pg 15 0 R /S /P >>
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<< /K 34 /P 92 0 R /Pg 15 0 R /S /P >>
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341 0 obj
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endobj
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endobj

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endobj
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385 0 obj
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<</K 20 /P 92 0 R /Pg 21 0 R /S /P >>
endobj
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393 0 obj
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endobj
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<< /K 11 /P 92 0 R /Pg 23 0 R /S /P >>
endobj
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<< /K 12 /P 92 0 R /Pg 23 0 R /S /P >>
endobj
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<< /K 13 /P 92 0 R /Pg 23 0 R /S /P >>
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<< /K 14 /P 92 0 R /Pg 23 0 R /S /P >>
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endobj
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<< /K 23 /P 92 0 R /Pg 23 0 R /S /P >>
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<< /K 25 /P 92 0 R /Pg 23 0 R /S /P >>
endobj
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<< /K 26 /P 92 0 R /Pg 23 0 R /S /P >>
endobj
417 0 obj
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endobj
418 0 obj
<< /K 28 /P 92 0 R /Pg 23 0 R /S /P >>
endobj
419 0 obj
<< /K 29 /P 92 0 R /Pg 23 0 R /S /P >>
endobj
420 0 obj
<< /K 30 /P 92 0 R /Pg 23 0 R /S /P >>
endobj

421 0 obj
<< /K 31 /P 92 0 R /Pg 23 0 R /S /P >>
endobj
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<< /K 32 /P 92 0 R /Pg 23 0 R /S /P >>
endobj
423 0 obj
<< /K 33 /P 92 0 R /Pg 23 0 R /S /P >>
endobj
424 0 obj
<< /K 34 /P 92 0 R /Pg 23 0 R /S /P >>
endobj
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<< /K [35 444 0 R 426 0 R 427 0 R 428 0 R 429 0 R 430 0 R 431 0 R 432 0 R 433 0 R 434 0 R 435 0 R 436 0 R 1252
0 R 440 0 R 441 0 R] /P 92 0 R /Pg 23 0 R /S /TextBox >>
endobj
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<< /K 38 /P 425 0 R /Pg 23 0 R /S /P >>
endobj
427 0 obj
<< /K 40 /P 425 0 R /Pg 23 0 R /S /P >>
endobj
428 0 obj
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429 0 obj
<< /K 44 /P 425 0 R /Pg 23 0 R /S /P >>
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430 0 obj
<< /K 46 /P 425 0 R /Pg 23 0 R /S /P >>
endobj
431 0 obj
<< /K 48 /P 425 0 R /Pg 23 0 R /S /P >>
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endobj
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endobj
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endobj
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<< /K 58 /P 425 0 R /Pg 23 0 R /S /P >>
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437 0 obj
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endobj
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endobj
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endobj
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endobj
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<< /K 9 /P 92 0 R /Pg 33 0 R /S /P >>
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<< /K 11 /P 92 0 R /Pg 33 0 R /S /P >>
endobj
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<< /K 12 /P 92 0 R /Pg 33 0 R /S /P >>
endobj
458 0 obj
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459 0 obj
<< /K 14 /P 92 0 R /Pg 33 0 R /S /P >>
endobj
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<< /K 15 /P 92 0 R /Pg 33 0 R /S /P >>

endobj
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462 0 obj
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<< /K 2 /P 92 0 R /Pg 35 0 R /S /P >>
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464 0 obj
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endobj
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<< /K 16 /P 92 0 R /Pg 35 0 R /S /P >>
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<< /K 17 /P 92 0 R /Pg 35 0 R /S /P >>
endobj
479 0 obj
<< /K 18 /P 92 0 R /Pg 35 0 R /S /P >>
endobj
480 0 obj
<< /K 19 /P 92 0 R /Pg 35 0 R /S /P >>

endobj
481 0 obj
<< /K 20 /P 92 0 R /Pg 35 0 R /S /H2 >>
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<< /K 22 /P 92 0 R /Pg 35 0 R /S /P >>
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<< /K [23 << /MCID 0 /Pg 37 0 R /Type /MCR >>] /P 92 0 R /Pg 35 0 R /S /P >>
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<< /K 24 /P 92 0 R /Pg 35 0 R /S /P >>
endobj
485 0 obj
<< /K 1 /P 92 0 R /Pg 37 0 R /S /P >>
endobj
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<< /K 3 /P 92 0 R /Pg 37 0 R /S /P >>
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487 0 obj
<< /K 4 /P 92 0 R /Pg 37 0 R /S /P >>
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493 0 obj
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494 0 obj
<< /K 11 /P 92 0 R /Pg 37 0 R /S /P >>
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495 0 obj
<< /K 12 /P 92 0 R /Pg 37 0 R /S /P >>
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<< /K 13 /P 92 0 R /Pg 37 0 R /S /P >>
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<< /K 14 /P 92 0 R /Pg 37 0 R /S /P >>
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endobj
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endobj
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<< /K 20 /P 92 0 R /Pg 37 0 R /S /P >>
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<< /K 21 /P 92 0 R /Pg 37 0 R /S /P >>
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504 0 obj
<< /K 22 /P 92 0 R /Pg 37 0 R /S /P >>
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507 0 obj
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endobj
508 0 obj
<< /K [30 31] /P 92 0 R /Pg 37 0 R /S /P >>
endobj
509 0 obj
<< /K 5 /P 92 0 R /Pg 39 0 R /S /P >>
endobj
510 0 obj
<< /K 8 /P 1254 0 R /Pg 39 0 R /S /LBody >>
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511 0 obj
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512 0 obj
<< /K 13 /P 92 0 R /Pg 39 0 R /S /P >>
endobj
513 0 obj
<< /K 14 /P 92 0 R /Pg 39 0 R /S /P >>
endobj
514 0 obj
<< /K 15 /P 92 0 R /Pg 39 0 R /S /P >>
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515 0 obj
<< /K [16 516 0 R 18] /P 92 0 R /Pg 39 0 R /S /H2 >>
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516 0 obj
<< /K 17 /P 515 0 R /Pg 39 0 R /S /Span >>
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542 0 obj
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<< /K 14 /P 92 0 R /Pg 41 0 R /S /P >>
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544 0 obj
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545 0 obj
<< /K 16 /P 92 0 R /Pg 41 0 R /S /H2 >>
endobj
546 0 obj
<< /K 17 /P 92 0 R /Pg 41 0 R /S /P >>
endobj
547 0 obj
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endobj
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<< /K 20 /P 92 0 R /Pg 41 0 R /S /P >>
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<< /K [22 << /MCID 0 /Pg 43 0 R /Type /MCR >>] /P 92 0 R /Pg 41 0 R /S /P >>
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<< /K 23 /P 92 0 R /Pg 41 0 R /S /P >>
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552 0 obj
<< /K 24 /P 92 0 R /Pg 41 0 R /S /P >>
endobj
553 0 obj
<< /K 25 /P 92 0 R /Pg 41 0 R /S /P >>
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559 0 obj
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<< /K 8 /P 92 0 R /Pg 43 0 R /S /P >>

endobj
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562 0 obj
<< /K 10 /P 92 0 R /Pg 43 0 R /S /P >>
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577 0 obj
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endobj
578 0 obj
<< /K 46 /P 1470 0 R /Pg 43 0 R /S /P >>
endobj
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<< /K 48 /P 1470 0 R /Pg 43 0 R /S /P >>
endobj
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<< /K 50 /P 1470 0 R /Pg 43 0 R /S /P >>

endobj
581 0 obj
<< /K 52 /P 1471 0 R /Pg 43 0 R /S /P >>
endobj
582 0 obj
<< /K 53 /P 1472 0 R /Pg 43 0 R /S /P >>
endobj
583 0 obj
<< /K 54 /P 1473 0 R /Pg 43 0 R /S /P >>
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584 0 obj
<< /K 55 /P 1473 0 R /Pg 43 0 R /S /P >>
endobj
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<< /K 56 /P 1473 0 R /Pg 43 0 R /S /P >>
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<< /K 57 /P 1473 0 R /Pg 43 0 R /S /P >>
endobj
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<< /K 58 /P 1473 0 R /Pg 43 0 R /S /P >>
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588 0 obj
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<< /K 62 /P 1475 0 R /Pg 43 0 R /S /P >>
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<< /K 83 /P 92 0 R /Pg 43 0 R /S /P >>
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endobj
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<< /K 1 /P 1480 0 R /Pg 45 0 R /S /P >>
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609 0 obj
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610 0 obj
<< /K 7 /P 1481 0 R /Pg 45 0 R /S /P >>
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611 0 obj
<< /K 8 /P 1482 0 R /Pg 45 0 R /S /P >>
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612 0 obj
<< /K 9 /P 1483 0 R /Pg 45 0 R /S /P >>
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614 0 obj
<< /K 11 /P 1484 0 R /Pg 45 0 R /S /P >>
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<< /K 19 /P 1485 0 R /Pg 45 0 R /S /P >>
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endobj
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<< /K 27 /P 1488 0 R /Pg 45 0 R /S /P >>
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625 0 obj
<< /K 28 /P 1489 0 R /Pg 45 0 R /S /P >>
endobj
626 0 obj
<< /K 29 /P 1489 0 R /Pg 45 0 R /S /P >>
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<< /K 26 /P 1453 0 R /Pg 51 0 R /S /P >>

endobj
881 0 obj
<< /K 28 /P 1453 0 R /Pg 51 0 R /S /P >>
endobj
882 0 obj
<< /K 30 /P 1453 0 R /Pg 51 0 R /S /P >>
endobj
883 0 obj
<< /K 32 /P 1454 0 R /Pg 51 0 R /S /P >>
endobj
884 0 obj
<< /K 33 /P 1455 0 R /Pg 51 0 R /S /P >>
endobj
885 0 obj
<< /K 34 /P 1456 0 R /Pg 51 0 R /S /P >>
endobj
886 0 obj
<< /K 35 /P 1456 0 R /Pg 51 0 R /S /P >>
endobj
887 0 obj
<< /K 36 /P 1456 0 R /Pg 51 0 R /S /P >>
endobj
888 0 obj
<< /K 39 /P 1457 0 R /Pg 51 0 R /S /P >>
endobj
889 0 obj
<< /K 41 /P 1457 0 R /Pg 51 0 R /S /P >>
endobj
890 0 obj
<< /K 43 /P 1457 0 R /Pg 51 0 R /S /P >>
endobj
891 0 obj
<< /K 45 /P 1458 0 R /Pg 51 0 R /S /P >>
endobj
892 0 obj
<< /K 46 /P 1459 0 R /Pg 51 0 R /S /P >>
endobj
893 0 obj
<< /K 47 /P 1459 0 R /Pg 51 0 R /S /P >>
endobj
894 0 obj
<< /K 48 /P 1459 0 R /Pg 51 0 R /S /P >>
endobj
895 0 obj
<< /K 49 /P 1459 0 R /Pg 51 0 R /S /P >>
endobj
896 0 obj
<< /K 50 /P 1460 0 R /Pg 51 0 R /S /P >>
endobj
897 0 obj
<< /K 53 /P 1461 0 R /Pg 51 0 R /S /P >>
endobj
898 0 obj
<< /K 55 /P 1462 0 R /Pg 51 0 R /S /P >>
endobj
899 0 obj
<< /K 56 /P 1462 0 R /Pg 51 0 R /S /P >>
endobj
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<< /K 57 /P 1462 0 R /Pg 51 0 R /S /P >>

endobj
901 0 obj
<< /K 58 /P 1463 0 R /Pg 51 0 R /S /P >>
endobj
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<< /K 59 /P 1463 0 R /Pg 51 0 R /S /P >>
endobj
903 0 obj
<< /K 60 /P 1463 0 R /Pg 51 0 R /S /P >>
endobj
904 0 obj
<< /K 61 /P 1463 0 R /Pg 51 0 R /S /P >>
endobj
905 0 obj
<< /K 62 /P 1463 0 R /Pg 51 0 R /S /P >>
endobj
906 0 obj
<< /K 63 /P 1463 0 R /Pg 51 0 R /S /P >>
endobj
907 0 obj
<< /K 64 /P 1463 0 R /Pg 51 0 R /S /P >>
endobj
908 0 obj
<< /K 65 /P 1463 0 R /Pg 51 0 R /S /P >>
endobj
909 0 obj
<< /K 66 /P 1464 0 R /Pg 51 0 R /S /P >>
endobj
910 0 obj
<< /K 67 /P 1464 0 R /Pg 51 0 R /S /P >>
endobj
911 0 obj
<< /K 68 /P 1464 0 R /Pg 51 0 R /S /P >>
endobj
912 0 obj
<< /K 70 /P 92 0 R /Pg 51 0 R /S /P >>
endobj
913 0 obj
<< /K 72 /P 92 0 R /Pg 51 0 R /S /P >>
endobj
914 0 obj
<< /K 74 /P 92 0 R /Pg 51 0 R /S /P >>
endobj
915 0 obj
<< /K 75 /P 92 0 R /Pg 51 0 R /S /P >>
endobj
916 0 obj
<< /K 76 /P 92 0 R /Pg 51 0 R /S /P >>
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917 0 obj
<< /K 77 /P 92 0 R /Pg 51 0 R /S /P >>
endobj
918 0 obj
<< /K 78 /P 92 0 R /Pg 51 0 R /S /P >>
endobj
919 0 obj
<< /K 79 /P 92 0 R /Pg 51 0 R /S /P >>
endobj
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<< /K 80 /P 92 0 R /Pg 51 0 R /S /P >>

endobj
921 0 obj
<< /K 81 /P 92 0 R /Pg 51 0 R /S /P >>
endobj
922 0 obj
<< /K 82 /P 92 0 R /Pg 51 0 R /S /P >>
endobj
923 0 obj
<< /K 83 /P 92 0 R /Pg 51 0 R /S /P >>
endobj
924 0 obj
<< /K 84 /P 92 0 R /Pg 51 0 R /S /P >>
endobj
925 0 obj
<< /K 0 /P 92 0 R /Pg 53 0 R /S /P >>
endobj
926 0 obj
<< /K 1 /P 92 0 R /Pg 53 0 R /S /P >>
endobj
927 0 obj
<< /K 2 /P 92 0 R /Pg 53 0 R /S /P >>
endobj
928 0 obj
<< /K 3 /P 92 0 R /Pg 53 0 R /S /P >>
endobj
929 0 obj
<< /K 4 /P 92 0 R /Pg 53 0 R /S /P >>
endobj
930 0 obj
<< /K 5 /P 92 0 R /Pg 53 0 R /S /P >>
endobj
931 0 obj
<< /K 6 /P 92 0 R /Pg 53 0 R /S /P >>
endobj
932 0 obj
<< /K 7 /P 92 0 R /Pg 53 0 R /S /P >>
endobj
933 0 obj
<< /K [8 934 0 R 15 16] /P 92 0 R /Pg 53 0 R /S /P >>
endobj
934 0 obj
<< /K [9 << /Obj 87 0 R /Pg 53 0 R /Type /OBJR >>] /P 933 0 R /Pg 53 0 R /S /Link >>
endobj
935 0 obj
<< /K 11 /P 92 0 R /Pg 53 0 R /S /P >>
endobj
936 0 obj
<< /K 12 /P 92 0 R /Pg 53 0 R /S /P >>
endobj
937 0 obj
<< /K 13 /P 92 0 R /Pg 53 0 R /S /H2 >>
endobj
938 0 obj
<< /K 14 /P 92 0 R /Pg 53 0 R /S /P >>
endobj
939 0 obj
<< /K 0 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
940 0 obj
<< /K 2 /P 92 0 R /Pg 56 0 R /S /P >>

endobj
941 0 obj
<< /K 3 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
942 0 obj
<< /K 4 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
943 0 obj
<< /K 5 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
944 0 obj
<< /K 6 /P 92 0 R /Pg 56 0 R /S /H1 >>
endobj
945 0 obj
<< /K 7 /P 92 0 R /Pg 56 0 R /S /H2 >>
endobj
946 0 obj
<< /K 8 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
947 0 obj
<< /K 9 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
948 0 obj
<< /K 10 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
949 0 obj
<< /K 12 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
950 0 obj
<< /K 13 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
951 0 obj
<< /K 14 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
952 0 obj
<< /K 16 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
953 0 obj
<< /K 17 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
954 0 obj
<< /K 18 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
955 0 obj
<< /K 20 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
956 0 obj
<< /K 22 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
957 0 obj
<< /K [23 << /MCID 0 /Pg 58 0 R /Type /MCR >>] /P 92 0 R /Pg 56 0 R /S /P >>
endobj
958 0 obj
<< /K 24 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
959 0 obj
<< /K 25 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
960 0 obj
<< /K 26 /P 92 0 R /Pg 56 0 R /S /P >>

endobj
961 0 obj
<< /K 27 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
962 0 obj
<< /K 28 /P 92 0 R /Pg 56 0 R /S /P >>
endobj
963 0 obj
<< /K 1 /P 92 0 R /Pg 58 0 R /S /P >>
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964 0 obj
<< /K 2 /P 92 0 R /Pg 58 0 R /S /P >>
endobj
965 0 obj
<< /K 4 /P 92 0 R /Pg 58 0 R /S /P >>
endobj
966 0 obj
<< /K 6 /P 1309 0 R /Pg 58 0 R /S /P >>
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967 0 obj
<< /K 9 /P 1310 0 R /Pg 58 0 R /S /P >>
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968 0 obj
<< /K 12 /P 1311 0 R /Pg 58 0 R /S /P >>
endobj
969 0 obj
<< /K 15 /P 1312 0 R /Pg 58 0 R /S /P >>
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970 0 obj
<< /K 19 /P 1313 0 R /Pg 58 0 R /S /P >>
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<< /K 21 /P 1314 0 R /Pg 58 0 R /S /P >>
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972 0 obj
<< /K 22 /P 1315 0 R /Pg 58 0 R /S /P >>
endobj
973 0 obj
<< /K 23 /P 1316 0 R /Pg 58 0 R /S /P >>
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974 0 obj
<< /K 24 /P 1317 0 R /Pg 58 0 R /S /P >>
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<< /K 27 /P 1318 0 R /Pg 58 0 R /S /P >>
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976 0 obj
<< /K 29 /P 1318 0 R /Pg 58 0 R /S /P >>
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977 0 obj
<< /K 31 /P 1319 0 R /Pg 58 0 R /S /P >>
endobj
978 0 obj
<< /K 32 /P 1320 0 R /Pg 58 0 R /S /P >>
endobj
979 0 obj
<< /K 33 /P 1321 0 R /Pg 58 0 R /S /P >>
endobj
980 0 obj
<< /K 34 /P 1322 0 R /Pg 58 0 R /S /P >>

endobj
981 0 obj
<< /K 37 /P 1323 0 R /Pg 58 0 R /S /P >>
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982 0 obj
<< /K 39 /P 1324 0 R /Pg 58 0 R /S /P >>
endobj
983 0 obj
<< /K 40 /P 1325 0 R /Pg 58 0 R /S /P >>
endobj
984 0 obj
<< /K 41 /P 1326 0 R /Pg 58 0 R /S /P >>
endobj
985 0 obj
<< /K 42 /P 1327 0 R /Pg 58 0 R /S /P >>
endobj
986 0 obj
<< /K 43 /P 1327 0 R /Pg 58 0 R /S /P >>
endobj
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<< /K 46 /P 1328 0 R /Pg 58 0 R /S /P >>
endobj
988 0 obj
<< /K 48 /P 1329 0 R /Pg 58 0 R /S /P >>
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<< /K 49 /P 1330 0 R /Pg 58 0 R /S /P >>
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990 0 obj
<< /K 50 /P 1331 0 R /Pg 58 0 R /S /P >>
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991 0 obj
<< /K 51 /P 1332 0 R /Pg 58 0 R /S /P >>
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992 0 obj
<< /K 52 /P 1332 0 R /Pg 58 0 R /S /P >>
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993 0 obj
<< /K 55 /P 1333 0 R /Pg 58 0 R /S /P >>
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<< /K 57 /P 1333 0 R /Pg 58 0 R /S /P >>
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<< /K 59 /P 1334 0 R /Pg 58 0 R /S /P >>
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<< /K 60 /P 1335 0 R /Pg 58 0 R /S /P >>
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997 0 obj
<< /K 61 /P 1336 0 R /Pg 58 0 R /S /P >>
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998 0 obj
<< /K 62 /P 1337 0 R /Pg 58 0 R /S /P >>
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999 0 obj
<< /K 63 /P 1337 0 R /Pg 58 0 R /S /P >>
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1000 0 obj
<< /K 66 /P 1338 0 R /Pg 58 0 R /S /P >>

endobj
1001 0 obj
<< /K 68 /P 1338 0 R /Pg 58 0 R /S /P >>
endobj
1002 0 obj
<< /K 70 /P 1339 0 R /Pg 58 0 R /S /P >>
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1003 0 obj
<< /K 71 /P 1340 0 R /Pg 58 0 R /S /P >>
endobj
1004 0 obj
<< /K 72 /P 1341 0 R /Pg 58 0 R /S /P >>
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1005 0 obj
<< /K 73 /P 1342 0 R /Pg 58 0 R /S /P >>
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1006 0 obj
<< /K 74 /P 1342 0 R /Pg 58 0 R /S /P >>
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1007 0 obj
<< /K 77 /P 1343 0 R /Pg 58 0 R /S /P >>
endobj
1008 0 obj
<< /K 79 /P 1344 0 R /Pg 58 0 R /S /P >>
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1009 0 obj
<< /K 80 /P 1345 0 R /Pg 58 0 R /S /P >>
endobj
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<< /K 81 /P 1346 0 R /Pg 58 0 R /S /P >>
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1011 0 obj
<< /K 82 /P 1347 0 R /Pg 58 0 R /S /P >>
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1012 0 obj
<< /K 85 /P 1348 0 R /Pg 58 0 R /S /P >>
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1013 0 obj
<< /K 87 /P 1348 0 R /Pg 58 0 R /S /P >>
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1014 0 obj
<< /K 89 /P 1349 0 R /Pg 58 0 R /S /P >>
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1015 0 obj
<< /K 90 /P 1350 0 R /Pg 58 0 R /S /P >>
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1016 0 obj
<< /K 91 /P 1351 0 R /Pg 58 0 R /S /P >>
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<< /K 92 /P 1352 0 R /Pg 58 0 R /S /P >>
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1018 0 obj
<< /K 95 /P 1353 0 R /Pg 58 0 R /S /P >>
endobj
1019 0 obj
<< /K 97 /P 1353 0 R /Pg 58 0 R /S /P >>
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1020 0 obj
<< /K 99 /P 1354 0 R /Pg 58 0 R /S /P >>

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<< /K 101 /P 1356 0 R /Pg 58 0 R /S /P >>
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1023 0 obj
<< /K 102 /P 1357 0 R /Pg 58 0 R /S /P >>
endobj
1024 0 obj
<< /K 105 /P 1358 0 R /Pg 58 0 R /S /P >>
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1025 0 obj
<< /K 107 /P 1358 0 R /Pg 58 0 R /S /P >>
endobj
1026 0 obj
<< /K 109 /P 1359 0 R /Pg 58 0 R /S /P >>
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1027 0 obj
<< /K 110 /P 1360 0 R /Pg 58 0 R /S /P >>
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1028 0 obj
<< /K 111 /P 1361 0 R /Pg 58 0 R /S /P >>
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<< /K 112 /P 1362 0 R /Pg 58 0 R /S /P >>
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1030 0 obj
<< /K 115 /P 1363 0 R /Pg 58 0 R /S /P >>
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1031 0 obj
<< /K 117 /P 1364 0 R /Pg 58 0 R /S /P >>
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1032 0 obj
<< /K 118 /P 1365 0 R /Pg 58 0 R /S /P >>
endobj
1033 0 obj
<< /K 119 /P 1366 0 R /Pg 58 0 R /S /P >>
endobj
1034 0 obj
<< /K 120 /P 1367 0 R /Pg 58 0 R /S /P >>
endobj
1035 0 obj
<< /K 121 /P 1367 0 R /Pg 58 0 R /S /P >>
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1036 0 obj
<< /K 124 /P 1368 0 R /Pg 58 0 R /S /P >>
endobj
1037 0 obj
<< /K 126 /P 1368 0 R /Pg 58 0 R /S /P >>
endobj
1038 0 obj
<< /K 128 /P 1369 0 R /Pg 58 0 R /S /P >>
endobj
1039 0 obj
<< /K 129 /P 1370 0 R /Pg 58 0 R /S /P >>
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1040 0 obj
<< /K 130 /P 1371 0 R /Pg 58 0 R /S /P >>

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1041 0 obj
<< /K 131 /P 1372 0 R /Pg 58 0 R /S /P >>
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1042 0 obj
<< /K 132 /P 1372 0 R /Pg 58 0 R /S /P >>
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1043 0 obj
<< /K 135 /P 1373 0 R /Pg 58 0 R /S /P >>
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<< /K 137 /P 1374 0 R /Pg 58 0 R /S /P >>
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<< /K 138 /P 1375 0 R /Pg 58 0 R /S /P >>
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1046 0 obj
<< /K 139 /P 1376 0 R /Pg 58 0 R /S /P >>
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1047 0 obj
<< /K 140 /P 1377 0 R /Pg 58 0 R /S /P >>
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1048 0 obj
<< /K 143 /P 1378 0 R /Pg 58 0 R /S /P >>
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<< /K 145 /P 1378 0 R /Pg 58 0 R /S /P >>
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<< /K 147 /P 1378 0 R /Pg 58 0 R /S /P >>
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1051 0 obj
<< /K 149 /P 1379 0 R /Pg 58 0 R /S /P >>
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<< /K 150 /P 1380 0 R /Pg 58 0 R /S /P >>
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<< /K 151 /P 1381 0 R /Pg 58 0 R /S /P >>
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<< /K 152 /P 1382 0 R /Pg 58 0 R /S /P >>
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1057 0 obj
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1058 0 obj
<< /K 4 /P 1385 0 R /Pg 60 0 R /S /P >>
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<< /K 5 /P 1386 0 R /Pg 60 0 R /S /P >>
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1060 0 obj
<< /K 6 /P 1387 0 R /Pg 60 0 R /S /P >>

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1061 0 obj
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<< /K 10 /P 1388 0 R /Pg 60 0 R /S /P >>
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1064 0 obj
<< /K 13 /P 1390 0 R /Pg 60 0 R /S /P >>
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1065 0 obj
<< /K 14 /P 1391 0 R /Pg 60 0 R /S /P >>
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<< /K 24 /P 1397 0 R /Pg 60 0 R /S /P >>
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1073 0 obj
<< /K 25 /P 1397 0 R /Pg 60 0 R /S /P >>
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1079 0 obj
<< /K 34 /P 1402 0 R /Pg 60 0 R /S /P >>
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1080 0 obj
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endobj
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<< /K 39 /P 1404 0 R /Pg 60 0 R /S /P >>
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1082 0 obj
<< /K 40 /P 1405 0 R /Pg 60 0 R /S /P >>
endobj
1083 0 obj
<< /K 41 /P 1406 0 R /Pg 60 0 R /S /P >>
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1084 0 obj
<< /K 42 /P 1407 0 R /Pg 60 0 R /S /P >>
endobj
1085 0 obj
<< /K 43 /P 1407 0 R /Pg 60 0 R /S /P >>
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1086 0 obj
<< /K 46 /P 1408 0 R /Pg 60 0 R /S /P >>
endobj
1087 0 obj
<< /K 48 /P 1409 0 R /Pg 60 0 R /S /P >>
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1088 0 obj
<< /K 49 /P 1410 0 R /Pg 60 0 R /S /P >>
endobj
1089 0 obj
<< /K 50 /P 1411 0 R /Pg 60 0 R /S /P >>
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1090 0 obj
<< /K 51 /P 1412 0 R /Pg 60 0 R /S /P >>
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1091 0 obj
<< /K 52 /P 1412 0 R /Pg 60 0 R /S /P >>
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1092 0 obj
<< /K 54 /P 92 0 R /Pg 60 0 R /S /P >>
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1093 0 obj
<< /K 57 /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1094 0 obj
<< /K 58 /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1095 0 obj
<< /K 60 /P 92 0 R /Pg 60 0 R /S /P >>
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1096 0 obj
<< /K 61 /P 92 0 R /Pg 60 0 R /S /P >>
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1097 0 obj
<< /K 62 /P 92 0 R /Pg 60 0 R /S /P >>
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<< /K 63 /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1099 0 obj
<< /K 65 /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1100 0 obj
<< /K 67 /P 92 0 R /Pg 60 0 R /S /P >>

endobj
1101 0 obj
<< /K 68 /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1102 0 obj
<< /K 69 /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1103 0 obj
<< /K 70 /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1104 0 obj
<< /K 71 /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1105 0 obj
<< /K 72 /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1106 0 obj
<< /K 73 /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1107 0 obj
<< /K 74 /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1108 0 obj
<< /K 75 /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1109 0 obj
<< /K [76 77] /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1110 0 obj
<< /K 78 /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1111 0 obj
<< /K [79 80] /P 92 0 R /Pg 60 0 R /S /P >>
endobj
1112 0 obj
<< /K 0 /P 92 0 R /Pg 62 0 R /S /H2 >>
endobj
1113 0 obj
<< /K 2 /P 92 0 R /Pg 62 0 R /S /P >>
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1114 0 obj
<< /K 3 /P 92 0 R /Pg 62 0 R /S /P >>
endobj
1115 0 obj
<< /K 4 /P 92 0 R /Pg 62 0 R /S /P >>
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1116 0 obj
<< /K 5 /P 92 0 R /Pg 62 0 R /S /P >>
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1117 0 obj
<< /K 6 /P 92 0 R /Pg 62 0 R /S /P >>
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1118 0 obj
<< /K 8 /P 92 0 R /Pg 62 0 R /S /P >>
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<< /K 9 /P 92 0 R /Pg 62 0 R /S /P >>
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endobj
1121 0 obj
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1122 0 obj
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1123 0 obj
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1126 0 obj
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endobj
1127 0 obj
<< /K 19 /P 92 0 R /Pg 62 0 R /S /P >>
endobj
1128 0 obj
<< /K 20 /P 92 0 R /Pg 62 0 R /S /P >>
endobj
1129 0 obj
<< /K 22 /P 92 0 R /Pg 62 0 R /S /P >>
endobj
1130 0 obj
<< /K 23 /P 92 0 R /Pg 62 0 R /S /P >>
endobj
1131 0 obj
<< /K [24 << /MCID 0 /Pg 64 0 R /Type /MCR >>] /P 92 0 R /Pg 62 0 R /S /P >>
endobj
1132 0 obj
<< /K 25 /P 92 0 R /Pg 62 0 R /S /P >>
endobj
1133 0 obj
<< /K 26 /P 92 0 R /Pg 62 0 R /S /P >>
endobj
1134 0 obj
<< /K 27 /P 92 0 R /Pg 62 0 R /S /P >>
endobj
1135 0 obj
<< /K 28 /P 92 0 R /Pg 62 0 R /S /P >>
endobj
1136 0 obj
<< /K 29 /P 92 0 R /Pg 62 0 R /S /P >>
endobj
1137 0 obj
<< /K 1 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1138 0 obj
<< /K 3 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1139 0 obj
<< /K 4 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1140 0 obj
<< /K 5 /P 92 0 R /Pg 64 0 R /S /P >>

endobj
1141 0 obj
<< /K 6 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1142 0 obj
<< /K 7 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1143 0 obj
<< /K 8 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1144 0 obj
<< /K 9 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1145 0 obj
<< /K 10 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1146 0 obj
<< /K 11 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1147 0 obj
<< /K 12 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1148 0 obj
<< /K 13 /P 92 0 R /Pg 64 0 R /S /P >>
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<< /K 14 /P 92 0 R /Pg 64 0 R /S /P >>
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<< /K 15 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1151 0 obj
<< /K 16 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1152 0 obj
<< /K 17 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1153 0 obj
<< /K 18 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1154 0 obj
<< /K 19 /P 92 0 R /Pg 64 0 R /S /H2 >>
endobj
1155 0 obj
<< /K 20 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1156 0 obj
<< /K 21 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1157 0 obj
<< /K 22 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1158 0 obj
<< /K 23 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1159 0 obj
<< /K 24 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1160 0 obj
<< /K 25 /P 92 0 R /Pg 64 0 R /S /P >>

endobj
1161 0 obj
<< /K 26 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1162 0 obj
<< /K [27 << /MCID 0 /Pg 66 0 R /Type /MCR >>] /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1163 0 obj
<< /K 28 /P 92 0 R /Pg 64 0 R /S /P >>
endobj
1164 0 obj
<< /K 1 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1165 0 obj
<< /K 2 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1166 0 obj
<< /K 3 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1167 0 obj
<< /K 4 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1168 0 obj
<< /K 5 /P 92 0 R /Pg 66 0 R /S /H1 >>
endobj
1169 0 obj
<< /K 6 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1170 0 obj
<< /K 7 /P 92 0 R /Pg 66 0 R /S /H2 >>
endobj
1171 0 obj
<< /K 8 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1172 0 obj
<< /K 10 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1173 0 obj
<< /K 11 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1174 0 obj
<< /K 12 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1175 0 obj
<< /K 13 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1176 0 obj
<< /K 14 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1177 0 obj
<< /K 16 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1178 0 obj
<< /K 17 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1179 0 obj
<< /K 18 /P 92 0 R /Pg 66 0 R /S /P >>
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1180 0 obj
<< /K 19 /P 92 0 R /Pg 66 0 R /S /P >>

endobj
1181 0 obj
<< /K 20 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1182 0 obj
<< /K 21 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1183 0 obj
<< /K 22 /P 92 0 R /Pg 66 0 R /S /H2 >>
endobj
1184 0 obj
<< /K 23 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1185 0 obj
<< /K 24 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1186 0 obj
<< /K 25 /P 92 0 R /Pg 66 0 R /S /H2 >>
endobj
1187 0 obj
<< /K 26 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1188 0 obj
<< /K 27 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1189 0 obj
<< /K 28 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1190 0 obj
<< /K 29 /P 92 0 R /Pg 66 0 R /S /P >>
endobj
1191 0 obj
<< /K 0 /P 92 0 R /Pg 68 0 R /S /H2 >>
endobj
1192 0 obj
<< /K 1 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1193 0 obj
<< /K 2 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1194 0 obj
<< /K 3 /P 92 0 R /Pg 68 0 R /S /H2 >>
endobj
1195 0 obj
<< /K 4 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1196 0 obj
<< /K 5 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1197 0 obj
<< /K 6 /P 92 0 R /Pg 68 0 R /S /H2 >>
endobj
1198 0 obj
<< /K 7 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1199 0 obj
<< /K 8 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1200 0 obj
<< /K 9 /P 92 0 R /Pg 68 0 R /S /H1 >>

endobj
1201 0 obj
<< /K 10 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1202 0 obj
<< /K 11 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1203 0 obj
<< /K 12 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1204 0 obj
<< /K 13 /P 92 0 R /Pg 68 0 R /S /P >>
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1205 0 obj
<< /K 14 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1206 0 obj
<< /K 15 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1207 0 obj
<< /K 16 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1208 0 obj
<< /K 17 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1209 0 obj
<< /K 18 /P 92 0 R /Pg 68 0 R /S /H1 >>
endobj
1210 0 obj
<< /K 19 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1211 0 obj
<< /K 20 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1212 0 obj
<< /K 21 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1213 0 obj
<< /K 22 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1214 0 obj
<< /K 23 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1215 0 obj
<< /K 24 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1216 0 obj
<< /K 25 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1217 0 obj
<< /K 26 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1218 0 obj
<< /K 27 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1219 0 obj
<< /K 28 /P 92 0 R /Pg 68 0 R /S /P >>
endobj
1220 0 obj
<< /K 29 /P 92 0 R /Pg 68 0 R /S /P >>

endobj
1221 0 obj
<</K [1230 0 R 1231 0 R] /P 92 0 R /S /L >>
endobj
1222 0 obj
<</A 1232 0 R /K [1233 0 R 1234 0 R 1235 0 R 1236 0 R 1237 0 R 1238 0 R 1239 0 R] /P 92 0 R /S /Table >>
endobj
1223 0 obj
<</A 1240 0 R /K [1241 0 R 1242 0 R 1243 0 R 1244 0 R 1245 0 R] /P 92 0 R /S /Table >>
endobj
1224 0 obj
<</A 1246 0 R /K [1247 0 R 1248 0 R 1249 0 R 1250 0 R 1251 0 R] /P 92 0 R /S /Table >>
endobj
1225 0 obj
<</K 1253 0 R /P 92 0 R /S /L >>
endobj
1226 0 obj
<</K 1254 0 R /P 92 0 R /S /L >>
endobj
1227 0 obj
<</A 1255 0 R /K [1256 0 R 1257 0 R 1258 0 R 1259 0 R 1260 0 R 1261 0 R 1262 0 R 1263 0 R 1264 0 R 1265 0 R
1266 0 R 1267 0 R 1268 0 R 1269 0 R 1270 0 R 1271 0 R 1272 0 R] /P 92 0 R /S /Table >>
endobj
1228 0 obj
<</A 1273 0 R /K [1274 0 R 1275 0 R 1276 0 R 1277 0 R 1278 0 R 1279 0 R 1280 0 R 1281 0 R 1282 0 R 1283 0 R
1284 0 R 1285 0 R 1286 0 R] /P 92 0 R /S /Table >>
endobj
1229 0 obj
<</A 1287 0 R /K [1288 0 R 1289 0 R 1290 0 R 1291 0 R 1292 0 R 1293 0 R 1294 0 R 1295 0 R 1296 0 R 1297 0 R
1298 0 R 1299 0 R 1300 0 R 1301 0 R 1302 0 R 1303 0 R 1304 0 R 1305 0 R 1306 0 R 1307 0 R 1308 0 R] /P 92 0 R
/S /Table >>
endobj
1230 0 obj
<</K 113 0 R /P 1221 0 R /S /LI >>
endobj
1231 0 obj
<</K 114 0 R /P 1221 0 R /S /LI >>
endobj
1232 0 obj
<</BBox [128.688 0.0 559.502 729.144] /O /Layout /Placement /Block >>
endobj
1233 0 obj
<</K [1582 0 R 1583 0 R 1584 0 R] /P 1222 0 R /S /TR >>
endobj
1234 0 obj
<</K [1585 0 R 1586 0 R 1587 0 R 1588 0 R 1589 0 R] /P 1222 0 R /S /TR >>
endobj
1235 0 obj
<</K [1590 0 R 1591 0 R 1592 0 R] /P 1222 0 R /S /TR >>
endobj
1236 0 obj
<</K [1593 0 R 1594 0 R 1595 0 R 1596 0 R 1597 0 R] /P 1222 0 R /S /TR >>
endobj
1237 0 obj
<</K [1598 0 R 1599 0 R 1600 0 R] /P 1222 0 R /S /TR >>
endobj
1238 0 obj
<</K [1601 0 R 1602 0 R 1603 0 R 1604 0 R 1605 0 R] /P 1222 0 R /S /TR >>
endobj
1239 0 obj

<< /K [1606 0 R 1607 0 R 1608 0 R] /P 1222 0 R /S /TR >>
endobj
1240 0 obj
<< /BBox [111.408 0.0 495.174 604.944] /O /Layout /Placement /Block >>
endobj
1241 0 obj
<< /K [1563 0 R 1564 0 R 1565 0 R] /P 1223 0 R /S /TR >>
endobj
1242 0 obj
<< /K [1566 0 R 1567 0 R 1568 0 R 1569 0 R 1570 0 R] /P 1223 0 R /S /TR >>
endobj
1243 0 obj
<< /K [1571 0 R 1572 0 R 1573 0 R 1574 0 R] /P 1223 0 R /S /TR >>
endobj
1244 0 obj
<< /K [1575 0 R 1576 0 R 1577 0 R 1578 0 R 1579 0 R] /P 1223 0 R /S /TR >>
endobj
1245 0 obj
<< /K [1580 0 R 1581 0 R] /P 1223 0 R /S /TR >>
endobj
1246 0 obj
<< /BBox [124.409 377.011 412.92 543.138] /O /Layout /Placement /Block >>
endobj
1247 0 obj
<< /K [1553 0 R 1554 0 R] /P 1224 0 R /S /TR >>
endobj
1248 0 obj
<< /K [1555 0 R 1556 0 R] /P 1224 0 R /S /TR >>
endobj
1249 0 obj
<< /K [1557 0 R 1558 0 R] /P 1224 0 R /S /TR >>
endobj
1250 0 obj
<< /K [1559 0 R 1560 0 R] /P 1224 0 R /S /TR >>
endobj
1251 0 obj
<< /K [1561 0 R 1562 0 R] /P 1224 0 R /S /TR >>
endobj
1252 0 obj
<< /K [1550 0 R 1551 0 R 1552 0 R] /P 425 0 R /S /L >>
endobj
1253 0 obj
<< /K 506 0 R /P 1225 0 R /S /LI >>
endobj
1254 0 obj
<< /K 510 0 R /P 1226 0 R /S /LI >>
endobj
1255 0 obj
<< /BBox [0.0 0.0 612.0 792.0] /O /Layout /Placement /Block >>
endobj
1256 0 obj
<< /K [1465 0 R 1466 0 R 1467 0 R 1468 0 R 1469 0 R] /P 1227 0 R /S /TR >>
endobj
1257 0 obj
<< /K [1470 0 R 1471 0 R 1472 0 R 1473 0 R 1474 0 R] /P 1227 0 R /S /TR >>
endobj
1258 0 obj
<< /K [1475 0 R 1476 0 R 1477 0 R 1478 0 R 1479 0 R] /P 1227 0 R /S /TR >>
endobj
1259 0 obj

<< /K [1480 0 R 1481 0 R 1482 0 R 1483 0 R 1484 0 R] /P 1227 0 R /S /TR >>
endobj
1260 0 obj
<< /K [1485 0 R 1486 0 R 1487 0 R 1488 0 R 1489 0 R] /P 1227 0 R /S /TR >>
endobj
1261 0 obj
<< /K [1490 0 R 1491 0 R 1492 0 R 1493 0 R 1494 0 R] /P 1227 0 R /S /TR >>
endobj
1262 0 obj
<< /K [1495 0 R 1496 0 R 1497 0 R 1498 0 R 1499 0 R] /P 1227 0 R /S /TR >>
endobj
1263 0 obj
<< /K [1500 0 R 1501 0 R 1502 0 R 1503 0 R 1504 0 R] /P 1227 0 R /S /TR >>
endobj
1264 0 obj
<< /K [1505 0 R 1506 0 R 1507 0 R 1508 0 R 1509 0 R] /P 1227 0 R /S /TR >>
endobj
1265 0 obj
<< /K [1510 0 R 1511 0 R 1512 0 R 1513 0 R 1514 0 R] /P 1227 0 R /S /TR >>
endobj
1266 0 obj
<< /K [1515 0 R 1516 0 R 1517 0 R 1518 0 R 1519 0 R] /P 1227 0 R /S /TR >>
endobj
1267 0 obj
<< /K [1520 0 R 1521 0 R 1522 0 R 1523 0 R 1524 0 R] /P 1227 0 R /S /TR >>
endobj
1268 0 obj
<< /K [1525 0 R 1526 0 R 1527 0 R 1528 0 R 1529 0 R] /P 1227 0 R /S /TR >>
endobj
1269 0 obj
<< /K [1530 0 R 1531 0 R 1532 0 R 1533 0 R 1534 0 R] /P 1227 0 R /S /TR >>
endobj
1270 0 obj
<< /K [1535 0 R 1536 0 R 1537 0 R 1538 0 R 1539 0 R] /P 1227 0 R /S /TR >>
endobj
1271 0 obj
<< /K [1540 0 R 1541 0 R 1542 0 R 1543 0 R 1544 0 R] /P 1227 0 R /S /TR >>
endobj
1272 0 obj
<< /K [1545 0 R 1546 0 R 1547 0 R 1548 0 R 1549 0 R] /P 1227 0 R /S /TR >>
endobj
1273 0 obj
<< /BBox [0.0 0.0 612.0 792.0] /O /Layout /Placement /Block >>
endobj
1274 0 obj
<< /K [1413 0 R 1414 0 R 1415 0 R 1416 0 R] /P 1228 0 R /S /TR >>
endobj
1275 0 obj
<< /K [1417 0 R 1418 0 R 1419 0 R 1420 0 R] /P 1228 0 R /S /TR >>
endobj
1276 0 obj
<< /K [1421 0 R 1422 0 R 1423 0 R 1424 0 R] /P 1228 0 R /S /TR >>
endobj
1277 0 obj
<< /K [1425 0 R 1426 0 R 1427 0 R 1428 0 R] /P 1228 0 R /S /TR >>
endobj
1278 0 obj
<< /K [1429 0 R 1430 0 R 1431 0 R 1432 0 R] /P 1228 0 R /S /TR >>
endobj
1279 0 obj

<< /K [1433 0 R 1434 0 R 1435 0 R 1436 0 R] /P 1228 0 R /S /TR >>
endobj
1280 0 obj
<< /K [1437 0 R 1438 0 R 1439 0 R 1440 0 R] /P 1228 0 R /S /TR >>
endobj
1281 0 obj
<< /K [1441 0 R 1442 0 R 1443 0 R 1444 0 R] /P 1228 0 R /S /TR >>
endobj
1282 0 obj
<< /K [1445 0 R 1446 0 R 1447 0 R 1448 0 R] /P 1228 0 R /S /TR >>
endobj
1283 0 obj
<< /K [1449 0 R 1450 0 R 1451 0 R 1452 0 R] /P 1228 0 R /S /TR >>
endobj
1284 0 obj
<< /K [1453 0 R 1454 0 R 1455 0 R 1456 0 R] /P 1228 0 R /S /TR >>
endobj
1285 0 obj
<< /K [1457 0 R 1458 0 R 1459 0 R 1460 0 R] /P 1228 0 R /S /TR >>
endobj
1286 0 obj
<< /K [1461 0 R 1462 0 R 1463 0 R 1464 0 R] /P 1228 0 R /S /TR >>
endobj
1287 0 obj
<< /BBox [0.0 0.0 612.0 792.0] /O /Layout /Placement /Block >>
endobj
1288 0 obj
<< /K [1309 0 R 1310 0 R 1311 0 R 1312 0 R] /P 1229 0 R /S /TR >>
endobj
1289 0 obj
<< /K [1313 0 R 1314 0 R 1315 0 R 1316 0 R 1317 0 R] /P 1229 0 R /S /TR >>
endobj
1290 0 obj
<< /K [1318 0 R 1319 0 R 1320 0 R 1321 0 R 1322 0 R] /P 1229 0 R /S /TR >>
endobj
1291 0 obj
<< /K [1323 0 R 1324 0 R 1325 0 R 1326 0 R 1327 0 R] /P 1229 0 R /S /TR >>
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1292 0 obj
<< /K [1328 0 R 1329 0 R 1330 0 R 1331 0 R 1332 0 R] /P 1229 0 R /S /TR >>
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1293 0 obj
<< /K [1333 0 R 1334 0 R 1335 0 R 1336 0 R 1337 0 R] /P 1229 0 R /S /TR >>
endobj
1294 0 obj
<< /K [1338 0 R 1339 0 R 1340 0 R 1341 0 R 1342 0 R] /P 1229 0 R /S /TR >>
endobj
1295 0 obj
<< /K [1343 0 R 1344 0 R 1345 0 R 1346 0 R 1347 0 R] /P 1229 0 R /S /TR >>
endobj
1296 0 obj
<< /K [1348 0 R 1349 0 R 1350 0 R 1351 0 R 1352 0 R] /P 1229 0 R /S /TR >>
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1297 0 obj
<< /K [1353 0 R 1354 0 R 1355 0 R 1356 0 R 1357 0 R] /P 1229 0 R /S /TR >>
endobj
1298 0 obj
<< /K [1358 0 R 1359 0 R 1360 0 R 1361 0 R 1362 0 R] /P 1229 0 R /S /TR >>
endobj
1299 0 obj

<< /K [1363 0 R 1364 0 R 1365 0 R 1366 0 R 1367 0 R] /P 1229 0 R /S /TR >>
endobj
1300 0 obj
<< /K [1368 0 R 1369 0 R 1370 0 R 1371 0 R 1372 0 R] /P 1229 0 R /S /TR >>
endobj
1301 0 obj
<< /K [1373 0 R 1374 0 R 1375 0 R 1376 0 R 1377 0 R] /P 1229 0 R /S /TR >>
endobj
1302 0 obj
<< /K [1378 0 R 1379 0 R 1380 0 R 1381 0 R 1382 0 R] /P 1229 0 R /S /TR >>
endobj
1303 0 obj
<< /K [1383 0 R 1384 0 R 1385 0 R 1386 0 R 1387 0 R] /P 1229 0 R /S /TR >>
endobj
1304 0 obj
<< /K [1388 0 R 1389 0 R 1390 0 R 1391 0 R 1392 0 R] /P 1229 0 R /S /TR >>
endobj
1305 0 obj
<< /K [1393 0 R 1394 0 R 1395 0 R 1396 0 R 1397 0 R] /P 1229 0 R /S /TR >>
endobj
1306 0 obj
<< /K [1398 0 R 1399 0 R 1400 0 R 1401 0 R 1402 0 R] /P 1229 0 R /S /TR >>
endobj
1307 0 obj
<< /K [1403 0 R 1404 0 R 1405 0 R 1406 0 R 1407 0 R] /P 1229 0 R /S /TR >>
endobj
1308 0 obj
<< /K [1408 0 R 1409 0 R 1410 0 R 1411 0 R 1412 0 R] /P 1229 0 R /S /TR >>
endobj
1309 0 obj
<< /K 966 0 R /P 1288 0 R /S /TH >>
endobj
1310 0 obj
<< /K 967 0 R /P 1288 0 R /S /TH >>
endobj
1311 0 obj
<< /K 968 0 R /P 1288 0 R /S /TH >>
endobj
1312 0 obj
<< /K 969 0 R /P 1288 0 R /S /TH >>
endobj
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<< /K 970 0 R /P 1289 0 R /S /TH >>
endobj
1314 0 obj
<< /K 971 0 R /P 1289 0 R /S /TD >>
endobj
1315 0 obj
<< /K 972 0 R /P 1289 0 R /S /TD >>
endobj
1316 0 obj
<< /K 973 0 R /P 1289 0 R /S /TD >>
endobj
1317 0 obj
<< /K 974 0 R /P 1289 0 R /S /TD >>
endobj
1318 0 obj
<< /K [975 0 R 976 0 R] /P 1290 0 R /S /TH >>
endobj
1319 0 obj

<< /K 977 0 R /P 1290 0 R /S /TD >>
endobj
1320 0 obj
<< /K 978 0 R /P 1290 0 R /S /TD >>
endobj
1321 0 obj
<< /K 979 0 R /P 1290 0 R /S /TD >>
endobj
1322 0 obj
<< /K 980 0 R /P 1290 0 R /S /TD >>
endobj
1323 0 obj
<< /K 981 0 R /P 1291 0 R /S /TH >>
endobj
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1326 0 obj
<< /K 984 0 R /P 1291 0 R /S /TD >>
endobj
1327 0 obj
<< /K [985 0 R 986 0 R] /P 1291 0 R /S /TD >>
endobj
1328 0 obj
<< /K 987 0 R /P 1292 0 R /S /TH >>
endobj
1329 0 obj
<< /K 988 0 R /P 1292 0 R /S /TD >>
endobj
1330 0 obj
<< /K 989 0 R /P 1292 0 R /S /TD >>
endobj
1331 0 obj
<< /K 990 0 R /P 1292 0 R /S /TD >>
endobj
1332 0 obj
<< /K [991 0 R 992 0 R] /P 1292 0 R /S /TD >>
endobj
1333 0 obj
<< /K [993 0 R 994 0 R] /P 1293 0 R /S /TH >>
endobj
1334 0 obj
<< /K 995 0 R /P 1293 0 R /S /TD >>
endobj
1335 0 obj
<< /K 996 0 R /P 1293 0 R /S /TD >>
endobj
1336 0 obj
<< /K 997 0 R /P 1293 0 R /S /TD >>
endobj
1337 0 obj
<< /K [998 0 R 999 0 R] /P 1293 0 R /S /TD >>
endobj
1338 0 obj
<< /K [1000 0 R 1001 0 R] /P 1294 0 R /S /TH >>
endobj
1339 0 obj

<< /K 1002 0 R /P 1294 0 R /S /TD >>
endobj
1340 0 obj
<< /K 1003 0 R /P 1294 0 R /S /TD >>
endobj
1341 0 obj
<< /K 1004 0 R /P 1294 0 R /S /TD >>
endobj
1342 0 obj
<< /K [1005 0 R 1006 0 R] /P 1294 0 R /S /TD >>
endobj
1343 0 obj
<< /K 1007 0 R /P 1295 0 R /S /TH >>
endobj
1344 0 obj
<< /K 1008 0 R /P 1295 0 R /S /TD >>
endobj
1345 0 obj
<< /K 1009 0 R /P 1295 0 R /S /TD >>
endobj
1346 0 obj
<< /K 1010 0 R /P 1295 0 R /S /TD >>
endobj
1347 0 obj
<< /K 1011 0 R /P 1295 0 R /S /TD >>
endobj
1348 0 obj
<< /K [1012 0 R 1013 0 R] /P 1296 0 R /S /TH >>
endobj
1349 0 obj
<< /K 1014 0 R /P 1296 0 R /S /TD >>
endobj
1350 0 obj
<< /K 1015 0 R /P 1296 0 R /S /TD >>
endobj
1351 0 obj
<< /K 1016 0 R /P 1296 0 R /S /TD >>
endobj
1352 0 obj
<< /K 1017 0 R /P 1296 0 R /S /TD >>
endobj
1353 0 obj
<< /K [1018 0 R 1019 0 R] /P 1297 0 R /S /TH >>
endobj
1354 0 obj
<< /K 1020 0 R /P 1297 0 R /S /TD >>
endobj
1355 0 obj
<< /K 1021 0 R /P 1297 0 R /S /TD >>
endobj
1356 0 obj
<< /K 1022 0 R /P 1297 0 R /S /TD >>
endobj
1357 0 obj
<< /K 1023 0 R /P 1297 0 R /S /TD >>
endobj
1358 0 obj
<< /K [1024 0 R 1025 0 R] /P 1298 0 R /S /TH >>
endobj
1359 0 obj

<< /K 1026 0 R /P 1298 0 R /S /TD >>
endobj
1360 0 obj
<< /K 1027 0 R /P 1298 0 R /S /TD >>
endobj
1361 0 obj
<< /K 1028 0 R /P 1298 0 R /S /TD >>
endobj
1362 0 obj
<< /K 1029 0 R /P 1298 0 R /S /TD >>
endobj
1363 0 obj
<< /K 1030 0 R /P 1299 0 R /S /TH >>
endobj
1364 0 obj
<< /K 1031 0 R /P 1299 0 R /S /TD >>
endobj
1365 0 obj
<< /K 1032 0 R /P 1299 0 R /S /TD >>
endobj
1366 0 obj
<< /K 1033 0 R /P 1299 0 R /S /TD >>
endobj
1367 0 obj
<< /K [1034 0 R 1035 0 R] /P 1299 0 R /S /TD >>
endobj
1368 0 obj
<< /K [1036 0 R 1037 0 R] /P 1300 0 R /S /TH >>
endobj
1369 0 obj
<< /K 1038 0 R /P 1300 0 R /S /TD >>
endobj
1370 0 obj
<< /K 1039 0 R /P 1300 0 R /S /TD >>
endobj
1371 0 obj
<< /K 1040 0 R /P 1300 0 R /S /TD >>
endobj
1372 0 obj
<< /K [1041 0 R 1042 0 R] /P 1300 0 R /S /TD >>
endobj
1373 0 obj
<< /K 1043 0 R /P 1301 0 R /S /TH >>
endobj
1374 0 obj
<< /K 1044 0 R /P 1301 0 R /S /TD >>
endobj
1375 0 obj
<< /K 1045 0 R /P 1301 0 R /S /TD >>
endobj
1376 0 obj
<< /K 1046 0 R /P 1301 0 R /S /TD >>
endobj
1377 0 obj
<< /K 1047 0 R /P 1301 0 R /S /TD >>
endobj
1378 0 obj
<< /K [1048 0 R 1049 0 R 1050 0 R] /P 1302 0 R /S /TH >>
endobj
1379 0 obj

<< /K 1051 0 R /P 1302 0 R /S /TD >>
endobj
1380 0 obj
<< /K 1052 0 R /P 1302 0 R /S /TD >>
endobj
1381 0 obj
<< /K 1053 0 R /P 1302 0 R /S /TD >>
endobj
1382 0 obj
<< /K 1054 0 R /P 1302 0 R /S /TD >>
endobj
1383 0 obj
<< /K 1056 0 R /P 1303 0 R /S /TH >>
endobj
1384 0 obj
<< /K 1057 0 R /P 1303 0 R /S /TD >>
endobj
1385 0 obj
<< /K 1058 0 R /P 1303 0 R /S /TD >>
endobj
1386 0 obj
<< /K 1059 0 R /P 1303 0 R /S /TD >>
endobj
1387 0 obj
<< /K [1060 0 R 1061 0 R] /P 1303 0 R /S /TD >>
endobj
1388 0 obj
<< /K 1062 0 R /P 1304 0 R /S /TH >>
endobj
1389 0 obj
<< /K 1063 0 R /P 1304 0 R /S /TD >>
endobj
1390 0 obj
<< /K 1064 0 R /P 1304 0 R /S /TD >>
endobj
1391 0 obj
<< /K 1065 0 R /P 1304 0 R /S /TD >>
endobj
1392 0 obj
<< /K [1066 0 R 1067 0 R] /P 1304 0 R /S /TD >>
endobj
1393 0 obj
<< /K 1068 0 R /P 1305 0 R /S /TH >>
endobj
1394 0 obj
<< /K 1069 0 R /P 1305 0 R /S /TD >>
endobj
1395 0 obj
<< /K 1070 0 R /P 1305 0 R /S /TD >>
endobj
1396 0 obj
<< /K 1071 0 R /P 1305 0 R /S /TD >>
endobj
1397 0 obj
<< /K [1072 0 R 1073 0 R] /P 1305 0 R /S /TD >>
endobj
1398 0 obj
<< /K 1074 0 R /P 1306 0 R /S /TH >>
endobj
1399 0 obj

<< /K 1075 0 R /P 1306 0 R /S /TD >>
endobj
1400 0 obj
<< /K 1076 0 R /P 1306 0 R /S /TD >>
endobj
1401 0 obj
<< /K 1077 0 R /P 1306 0 R /S /TD >>
endobj
1402 0 obj
<< /K [1078 0 R 1079 0 R] /P 1306 0 R /S /TD >>
endobj
1403 0 obj
<< /K 1080 0 R /P 1307 0 R /S /TH >>
endobj
1404 0 obj
<< /K 1081 0 R /P 1307 0 R /S /TD >>
endobj
1405 0 obj
<< /K 1082 0 R /P 1307 0 R /S /TD >>
endobj
1406 0 obj
<< /K 1083 0 R /P 1307 0 R /S /TD >>
endobj
1407 0 obj
<< /K [1084 0 R 1085 0 R] /P 1307 0 R /S /TD >>
endobj
1408 0 obj
<< /K 1086 0 R /P 1308 0 R /S /TH >>
endobj
1409 0 obj
<< /K 1087 0 R /P 1308 0 R /S /TD >>
endobj
1410 0 obj
<< /K 1088 0 R /P 1308 0 R /S /TD >>
endobj
1411 0 obj
<< /K 1089 0 R /P 1308 0 R /S /TD >>
endobj
1412 0 obj
<< /K [1090 0 R 1091 0 R] /P 1308 0 R /S /TD >>
endobj
1413 0 obj
<< /K [791 0 R 792 0 R 793 0 R] /P 1274 0 R /S /TH >>
endobj
1414 0 obj
<< /K 794 0 R /P 1274 0 R /S /TH >>
endobj
1415 0 obj
<< /K 795 0 R /P 1274 0 R /S /TH >>
endobj
1416 0 obj
<< /K [796 0 R 797 0 R] /P 1274 0 R /S /TH >>
endobj
1417 0 obj
<< /K [798 0 R 799 0 R 800 0 R] /P 1275 0 R /S /TH >>
endobj
1418 0 obj
<< /K 801 0 R /P 1275 0 R /S /TD >>
endobj
1419 0 obj

<< /K 802 0 R /P 1275 0 R /S /TD >>
endobj
1420 0 obj
<< /K [803 0 R 804 0 R 805 0 R] /P 1275 0 R /S /TD >>
endobj
1421 0 obj
<< /K [806 0 R 807 0 R 808 0 R] /P 1276 0 R /S /TH >>
endobj
1422 0 obj
<< /K 809 0 R /P 1276 0 R /S /TD >>
endobj
1423 0 obj
<< /K 810 0 R /P 1276 0 R /S /TD >>
endobj
1424 0 obj
<< /K [811 0 R 812 0 R 813 0 R] /P 1276 0 R /S /TD >>
endobj
1425 0 obj
<< /K [814 0 R 815 0 R 816 0 R] /P 1277 0 R /S /TH >>
endobj
1426 0 obj
<< /K 817 0 R /P 1277 0 R /S /TD >>
endobj
1427 0 obj
<< /K 818 0 R /P 1277 0 R /S /TD >>
endobj
1428 0 obj
<< /K [819 0 R 820 0 R] /P 1277 0 R /S /TD >>
endobj
1429 0 obj
<< /K 821 0 R /P 1278 0 R /S /TH >>
endobj
1430 0 obj
<< /K 822 0 R /P 1278 0 R /S /TD >>
endobj
1431 0 obj
<< /K [823 0 R 824 0 R 825 0 R 826 0 R 827 0 R] /P 1278 0 R /S /TD >>
endobj
1432 0 obj
<< /K [828 0 R 829 0 R 830 0 R 831 0 R 832 0 R 833 0 R] /P 1278 0 R /S /TD >>
endobj
1433 0 obj
<< /K [834 0 R 835 0 R 836 0 R] /P 1279 0 R /S /TH >>
endobj
1434 0 obj
<< /K 837 0 R /P 1279 0 R /S /TD >>
endobj
1435 0 obj
<< /K [838 0 R 839 0 R 840 0 R 841 0 R 842 0 R 843 0 R 844 0 R] /P 1279 0 R /S /TD >>
endobj
1436 0 obj
<< /K [845 0 R 846 0 R 847 0 R 848 0 R 849 0 R] /P 1279 0 R /S /TD >>
endobj
1437 0 obj
<< /K 850 0 R /P 1280 0 R /S /TH >>
endobj
1438 0 obj
<< /K 851 0 R /P 1280 0 R /S /TD >>
endobj
1439 0 obj

<< /K [852 0 R 853 0 R] /P 1280 0 R /S /TD >>
endobj
1440 0 obj
<< /K 854 0 R /P 1280 0 R /S /TD >>
endobj
1441 0 obj
<< /K [855 0 R 856 0 R 857 0 R] /P 1281 0 R /S /TH >>
endobj
1442 0 obj
<< /K 858 0 R /P 1281 0 R /S /TD >>
endobj
1443 0 obj
<< /K 859 0 R /P 1281 0 R /S /TD >>
endobj
1444 0 obj
<< /K [860 0 R 861 0 R] /P 1281 0 R /S /TD >>
endobj
1445 0 obj
<< /K [863 0 R 864 0 R 865 0 R] /P 1282 0 R /S /TH >>
endobj
1446 0 obj
<< /K 866 0 R /P 1282 0 R /S /TD >>
endobj
1447 0 obj
<< /K [867 0 R 868 0 R 869 0 R 870 0 R 871 0 R 872 0 R] /P 1282 0 R /S /TD >>
endobj
1448 0 obj
<< /K [873 0 R 874 0 R] /P 1282 0 R /S /TD >>
endobj
1449 0 obj
<< /K 875 0 R /P 1283 0 R /S /TH >>
endobj
1450 0 obj
<< /K 876 0 R /P 1283 0 R /S /TD >>
endobj
1451 0 obj
<< /K 877 0 R /P 1283 0 R /S /TD >>
endobj
1452 0 obj
<< /K [878 0 R 879 0 R] /P 1283 0 R /S /TD >>
endobj
1453 0 obj
<< /K [880 0 R 881 0 R 882 0 R] /P 1284 0 R /S /TH >>
endobj
1454 0 obj
<< /K 883 0 R /P 1284 0 R /S /TD >>
endobj
1455 0 obj
<< /K 884 0 R /P 1284 0 R /S /TD >>
endobj
1456 0 obj
<< /K [885 0 R 886 0 R 887 0 R] /P 1284 0 R /S /TD >>
endobj
1457 0 obj
<< /K [888 0 R 889 0 R 890 0 R] /P 1285 0 R /S /TH >>
endobj
1458 0 obj
<< /K 891 0 R /P 1285 0 R /S /TD >>
endobj
1459 0 obj

<< /K [892 0 R 893 0 R 894 0 R 895 0 R] /P 1285 0 R /S /TD >>
endobj
1460 0 obj
<< /K 896 0 R /P 1285 0 R /S /TD >>
endobj
1461 0 obj
<< /K 897 0 R /P 1286 0 R /S /TH >>
endobj
1462 0 obj
<< /K [898 0 R 899 0 R 900 0 R] /P 1286 0 R /S /TD >>
endobj
1463 0 obj
<< /K [901 0 R 902 0 R 903 0 R 904 0 R 905 0 R 906 0 R 907 0 R 908 0 R] /P 1286 0 R /S /TD >>
endobj
1464 0 obj
<< /K [909 0 R 910 0 R 911 0 R] /P 1286 0 R /S /TD >>
endobj
1465 0 obj
<< /K [567 0 R 568 0 R 569 0 R 570 0 R] /P 1256 0 R /S /TH >>
endobj
1466 0 obj
<< /K [571 0 R 572 0 R 573 0 R] /P 1256 0 R /S /TH >>
endobj
1467 0 obj
<< /K 574 0 R /P 1256 0 R /S /TH >>
endobj
1468 0 obj
<< /K 575 0 R /P 1256 0 R /S /TH >>
endobj
1469 0 obj
<< /K [576 0 R 577 0 R] /P 1256 0 R /S /TH >>
endobj
1470 0 obj
<< /K [578 0 R 579 0 R 580 0 R] /P 1257 0 R /S /TH >>
endobj
1471 0 obj
<< /K 581 0 R /P 1257 0 R /S /TD >>
endobj
1472 0 obj
<< /K 582 0 R /P 1257 0 R /S /TD >>
endobj
1473 0 obj
<< /K [583 0 R 584 0 R 585 0 R 586 0 R 587 0 R] /P 1257 0 R /S /TD >>
endobj
1474 0 obj
<< /K 588 0 R /P 1257 0 R /S /TD >>
endobj
1475 0 obj
<< /K [589 0 R 590 0 R 591 0 R 592 0 R] /P 1258 0 R /S /TH >>
endobj
1476 0 obj
<< /K 593 0 R /P 1258 0 R /S /TD >>
endobj
1477 0 obj
<< /K 594 0 R /P 1258 0 R /S /TD >>
endobj
1478 0 obj
<< /K 595 0 R /P 1258 0 R /S /TD >>
endobj
1479 0 obj

<< /K [596 0 R 597 0 R 598 0 R 599 0 R 600 0 R 601 0 R 602 0 R 603 0 R] /P 1258 0 R /S /TD >>
endobj
1480 0 obj
<< /K [607 0 R 608 0 R 609 0 R] /P 1259 0 R /S /TH >>
endobj
1481 0 obj
<< /K 610 0 R /P 1259 0 R /S /TD >>
endobj
1482 0 obj
<< /K 611 0 R /P 1259 0 R /S /TD >>
endobj
1483 0 obj
<< /K 612 0 R /P 1259 0 R /S /TD >>
endobj
1484 0 obj
<< /K [613 0 R 614 0 R 615 0 R 616 0 R 617 0 R] /P 1259 0 R /S /TD >>
endobj
1485 0 obj
<< /K [618 0 R 619 0 R 620 0 R 621 0 R] /P 1260 0 R /S /TH >>
endobj
1486 0 obj
<< /K 622 0 R /P 1260 0 R /S /TD >>
endobj
1487 0 obj
<< /K 623 0 R /P 1260 0 R /S /TD >>
endobj
1488 0 obj
<< /K 624 0 R /P 1260 0 R /S /TD >>
endobj
1489 0 obj
<< /K [625 0 R 626 0 R 627 0 R] /P 1260 0 R /S /TD >>
endobj
1490 0 obj
<< /K [628 0 R 629 0 R 630 0 R] /P 1261 0 R /S /TH >>
endobj
1491 0 obj
<< /K [631 0 R 632 0 R 633 0 R 634 0 R 635 0 R] /P 1261 0 R /S /TD >>
endobj
1492 0 obj
<< /K [636 0 R 637 0 R 638 0 R 639 0 R] /P 1261 0 R /S /TD >>
endobj
1493 0 obj
<< /K [640 0 R 641 0 R 642 0 R 643 0 R 644 0 R] /P 1261 0 R /S /TD >>
endobj
1494 0 obj
<< /K [645 0 R 646 0 R] /P 1261 0 R /S /TD >>
endobj
1495 0 obj
<< /K [647 0 R 648 0 R 649 0 R] /P 1262 0 R /S /TH >>
endobj
1496 0 obj
<< /K [650 0 R 651 0 R 652 0 R 653 0 R 654 0 R] /P 1262 0 R /S /TD >>
endobj
1497 0 obj
<< /K [655 0 R 656 0 R 657 0 R 658 0 R 659 0 R 660 0 R 661 0 R] /P 1262 0 R /S /TD >>
endobj
1498 0 obj
<< /K 662 0 R /P 1262 0 R /S /TD >>
endobj
1499 0 obj

<< /K [663 0 R 664 0 R 665 0 R 666 0 R 667 0 R 668 0 R 669 0 R 670 0 R] /P 1262 0 R /S /TD >>
endobj
1500 0 obj
<< /K 671 0 R /P 1263 0 R /S /TH >>
endobj
1501 0 obj
<< /K [672 0 R 673 0 R] /P 1263 0 R /S /TD >>
endobj
1502 0 obj
<< /K 674 0 R /P 1263 0 R /S /TD >>
endobj
1503 0 obj
<< /K 675 0 R /P 1263 0 R /S /TD >>
endobj
1504 0 obj
<< /K [676 0 R 677 0 R 678 0 R 679 0 R 680 0 R 681 0 R] /P 1263 0 R /S /TD >>
endobj
1505 0 obj
<< /K [682 0 R 683 0 R 684 0 R 685 0 R] /P 1264 0 R /S /TH >>
endobj
1506 0 obj
<< /K 686 0 R /P 1264 0 R /S /TD >>
endobj
1507 0 obj
<< /K 687 0 R /P 1264 0 R /S /TD >>
endobj
1508 0 obj
<< /K 688 0 R /P 1264 0 R /S /TD >>
endobj
1509 0 obj
<< /K [689 0 R 690 0 R 691 0 R 692 0 R 693 0 R 694 0 R] /P 1264 0 R /S /TD >>
endobj
1510 0 obj
<< /K [695 0 R 696 0 R 697 0 R] /P 1265 0 R /S /TH >>
endobj
1511 0 obj
<< /K 698 0 R /P 1265 0 R /S /TD >>
endobj
1512 0 obj
<< /K [699 0 R 700 0 R 701 0 R 702 0 R 703 0 R 704 0 R] /P 1265 0 R /S /TD >>
endobj
1513 0 obj
<< /K 705 0 R /P 1265 0 R /S /TD >>
endobj
1514 0 obj
<< /K [706 0 R 707 0 R] /P 1265 0 R /S /TD >>
endobj
1515 0 obj
<< /K [708 0 R 709 0 R 710 0 R] /P 1266 0 R /S /TH >>
endobj
1516 0 obj
<< /K 711 0 R /P 1266 0 R /S /TD >>
endobj
1517 0 obj
<< /K 712 0 R /P 1266 0 R /S /TD >>
endobj
1518 0 obj
<< /K [713 0 R 714 0 R 715 0 R] /P 1266 0 R /S /TD >>
endobj
1519 0 obj

<< /K [716 0 R 717 0 R] /P 1266 0 R /S /TD >>
endobj
1520 0 obj
<< /K [718 0 R 719 0 R 720 0 R 721 0 R] /P 1267 0 R /S /TH >>
endobj
1521 0 obj
<< /K 722 0 R /P 1267 0 R /S /TD >>
endobj
1522 0 obj
<< /K [723 0 R 724 0 R 725 0 R 726 0 R] /P 1267 0 R /S /TD >>
endobj
1523 0 obj
<< /K 727 0 R /P 1267 0 R /S /TD >>
endobj
1524 0 obj
<< /K [728 0 R 729 0 R 730 0 R 731 0 R 732 0 R] /P 1267 0 R /S /TD >>
endobj
1525 0 obj
<< /K [733 0 R 734 0 R 735 0 R 736 0 R] /P 1268 0 R /S /TH >>
endobj
1526 0 obj
<< /K 737 0 R /P 1268 0 R /S /TD >>
endobj
1527 0 obj
<< /K 738 0 R /P 1268 0 R /S /TD >>
endobj
1528 0 obj
<< /K 739 0 R /P 1268 0 R /S /TD >>
endobj
1529 0 obj
<< /K [740 0 R 741 0 R] /P 1268 0 R /S /TD >>
endobj
1530 0 obj
<< /K [742 0 R 743 0 R 744 0 R 745 0 R] /P 1269 0 R /S /TH >>
endobj
1531 0 obj
<< /K 746 0 R /P 1269 0 R /S /TD >>
endobj
1532 0 obj
<< /K 747 0 R /P 1269 0 R /S /TD >>
endobj
1533 0 obj
<< /K 748 0 R /P 1269 0 R /S /TD >>
endobj
1534 0 obj
<< /K [749 0 R 750 0 R 751 0 R 752 0 R] /P 1269 0 R /S /TD >>
endobj
1535 0 obj
<< /K [753 0 R 754 0 R 755 0 R 756 0 R] /P 1270 0 R /S /TH >>
endobj
1536 0 obj
<< /K 757 0 R /P 1270 0 R /S /TD >>
endobj
1537 0 obj
<< /K [758 0 R 759 0 R 760 0 R 761 0 R 762 0 R] /P 1270 0 R /S /TD >>
endobj
1538 0 obj
<< /K 763 0 R /P 1270 0 R /S /TD >>
endobj
1539 0 obj

<< /K 764 0 R /P 1270 0 R /S /TD >>
endobj
1540 0 obj
<< /K 765 0 R /P 1271 0 R /S /TH >>
endobj
1541 0 obj
<< /K [766 0 R 767 0 R 768 0 R] /P 1271 0 R /S /TD >>
endobj
1542 0 obj
<< /K [769 0 R 770 0 R] /P 1271 0 R /S /TD >>
endobj
1543 0 obj
<< /K 771 0 R /P 1271 0 R /S /TD >>
endobj
1544 0 obj
<< /K [772 0 R 773 0 R 774 0 R 775 0 R 776 0 R 777 0 R 778 0 R] /P 1271 0 R /S /TD >>
endobj
1545 0 obj
<< /K [779 0 R 780 0 R 781 0 R 782 0 R] /P 1272 0 R /S /TH >>
endobj
1546 0 obj
<< /K 783 0 R /P 1272 0 R /S /TD >>
endobj
1547 0 obj
<< /K 784 0 R /P 1272 0 R /S /TD >>
endobj
1548 0 obj
<< /K 785 0 R /P 1272 0 R /S /TD >>
endobj
1549 0 obj
<< /K [786 0 R 787 0 R] /P 1272 0 R /S /TD >>
endobj
1550 0 obj
<< /K 437 0 R /P 1252 0 R /S /LI >>
endobj
1551 0 obj
<< /K 438 0 R /P 1252 0 R /S /LI >>
endobj
1552 0 obj
<< /K 439 0 R /P 1252 0 R /S /LI >>
endobj
1553 0 obj
<< /K 283 0 R /P 1247 0 R /S /TH >>
endobj
1554 0 obj
<< /K [284 0 R 285 0 R] /P 1247 0 R /S /TH >>
endobj
1555 0 obj
<< /K 286 0 R /P 1248 0 R /S /TH >>
endobj
1556 0 obj
<< /K [287 0 R 288 0 R] /P 1248 0 R /S /TD >>
endobj
1557 0 obj
<< /K 289 0 R /P 1249 0 R /S /TH >>
endobj
1558 0 obj
<< /K [290 0 R 291 0 R] /P 1249 0 R /S /TD >>
endobj
1559 0 obj

<< /K 292 0 R /P 1250 0 R /S /TH >>
endobj
1560 0 obj
<< /K [293 0 R 294 0 R] /P 1250 0 R /S /TD >>
endobj
1561 0 obj
<< /K 295 0 R /P 1251 0 R /S /TH >>
endobj
1562 0 obj
<< /K [296 0 R 297 0 R] /P 1251 0 R /S /TD >>
endobj
1563 0 obj
<< /K [208 0 R 209 0 R] /P 1241 0 R /S /TH >>
endobj
1564 0 obj
<< /K 210 0 R /P 1241 0 R /S /TH >>
endobj
1565 0 obj
<< /K [211 0 R 212 0 R] /P 1241 0 R /S /TH >>
endobj
1566 0 obj
<< /K [213 0 R 214 0 R 215 0 R 216 0 R 273 0 R 217 0 R] /P 1242 0 R /S /TH >>
endobj
1567 0 obj
<< /K 218 0 R /P 1242 0 R /S /TD >>
endobj
1568 0 obj
<< /K 219 0 R /P 1242 0 R /S /TD >>
endobj
1569 0 obj
<< /K [220 0 R 221 0 R 222 0 R] /P 1242 0 R /S /TD >>
endobj
1570 0 obj
<< /K [223 0 R 224 0 R] /P 1242 0 R /S /TD >>
endobj
1571 0 obj
<< /K [225 0 R 226 0 R 227 0 R 228 0 R] /P 1243 0 R /S /TD >>
endobj
1572 0 obj
<< /K [229 0 R 230 0 R] /P 1243 0 R /S /TD >>
endobj
1573 0 obj
<< /K [231 0 R 232 0 R 233 0 R 234 0 R] /P 1243 0 R /S /TD >>
endobj
1574 0 obj
<< /K [235 0 R 236 0 R 237 0 R 238 0 R] /P 1243 0 R /S /TD >>
endobj
1575 0 obj
<< /K [239 0 R 240 0 R 241 0 R 242 0 R 243 0 R] /P 1244 0 R /S /TH >>
endobj
1576 0 obj
<< /K 244 0 R /P 1244 0 R /S /TD >>
endobj
1577 0 obj
<< /K [245 0 R 246 0 R] /P 1244 0 R /S /TD >>
endobj
1578 0 obj
<< /K [247 0 R 248 0 R 249 0 R 250 0 R 251 0 R 252 0 R] /P 1244 0 R /S /TD >>
endobj
1579 0 obj

<< /K [253 0 R 254 0 R 255 0 R 256 0 R 257 0 R 258 0 R] /P 1244 0 R /S /TD >>
endobj
1580 0 obj
<< /K [259 0 R 260 0 R 261 0 R 262 0 R] /P 1245 0 R /S /TD >>
endobj
1581 0 obj
<< /K [263 0 R 264 0 R 265 0 R] /P 1245 0 R /S /TD >>
endobj
1582 0 obj
<< /K [128 0 R 129 0 R] /P 1233 0 R /S /TH >>
endobj
1583 0 obj
<< /K 130 0 R /P 1233 0 R /S /TH >>
endobj
1584 0 obj
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2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100 mg of zonisamide.

Excipients of known effect:

Allura red (E129) and Sunset yellow (E110)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.

A size “1” white opaque body and a red opaque cap imprinted with “T” on cap and “20” on body with black ink containing white to off white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zonisamide Waymade hard capsules are indicated as:

- monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy (see section 5.1);
- adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above.

4.2 Posology and method of administration

Posology - Adults

Dosage escalation and maintenance

Zonisamide Waymade hard capsules may be taken as monotherapy or added to existing therapy in adults. The dose should be titrated on the basis of clinical effect. Recommended escalation and maintenance doses are given in Table 1. Some patients, especially those not taking CYP3A4-inducing agents, may respond to lower doses.

Withdrawal

When Zonisamide Waymade hard capsules treatment is to be discontinued, it should be withdrawn gradually (see section 4.4). In clinical studies of adult patients, dose reductions of 100 mg at weekly intervals have been used with concurrent adjustment of other antiepileptic medicine doses (where necessary).

Table 1. Adults – recommended dosage escalation and maintenance regimen

Treatment Regimen	Titration Phase			Usual Maintenance Dose
	Week 1 + 2	Week 3 + 4	Week 5 + 6	
Monotherapy Newly diagnosed adult patients				300 mg per day (once a day). If a higher dose is required: increase at two-weekly intervals in increments of 100 mg up to a maximum of 500 mg.
	100 mg/day (once a day)	200 mg /day (once a day)	300 mg / day (once a day)	
Adjunctive therapy - with	Week 1	Week 2	Week 3 to 5	300 to 500 mg per day

CYP3A4-inducing agents (see section 4.5)	50 mg/day (in two divided doses)	100 mg /day (in two divided doses)	Increase at weekly intervals in increments of 100 mg	(once a day or two divided doses).
- without CYP3A4-inducing agents; or with renal or hepatic impairment	Week 1 + 2	Week 3 + 4	Week 5 to 10	300 to 500 mg per day (once a day or two divided doses). Some patients may respond to lower doses.
	50 mg/day (in two divided doses)	100 mg / day (in two divided doses)	Increase at two-weekly intervals in increments of up to 100 mg	

General dosing recommendations for Zonisamide in special patient populations
Paediatric population (aged 6 years and above)

Dosage escalation and maintenance

Zonisamide Waymade hard capsules must be added to existing therapy for paediatric patients aged 6 years and above. The dose should be titrated on the basis of clinical effect. Recommended escalation and maintenance doses are given in Table 2. Some patients, especially those not taking CYP3A4-inducing agents, may respond to lower doses.

Physicians should draw the attention of paediatric patients and their parents/carers to the Patient Alert Box (in the package leaflet) on preventing heatstroke (see section 4.4: Paediatric population).

Table 2. Paediatric population (aged 6 years and above) – recommended dosage escalation and maintenance regimen

Treatment Regimen	Titration Phase		Usual Maintenance Dose	
	Adjunctive therapy - with CYP3A4-	Week 1	Weeks 2 to 8	Patients of weight 20 to 55 kg ^a

inducing agents (see section 4.5)	1 mg/kg/day (once a day)	Increase at weekly intervals in increments of 1 mg/kg	6 to 8 mg/kg/day (once a day)	300 - 500 mg/day (once a day)
- without CYP3A4-inducing agents	Week 1 + 2	Weeks \geq 3	6 to 8 mg/kg/day (once a day)	300 - 500 mg/day (once a day)
	1 mg/kg/day (once a day)	Increase at two-weekly intervals in increments of 1 mg/kg		

Note:

a. To ensure a therapeutic dose is maintained the weight of a child should be monitored and the dose reviewed as weight changes occur up to a weight of 55kg. The dose regime is 6-8 mg/kg/day up to a maximum dose of 500 mg/day.

The safety and efficacy of Zonisamide Waymade hard capsules in children aged below 6 years or those below 20 kg have not yet been established.

There are limited data from clinical studies in patients with a body weight of less than 20 kg. Therefore, children aged 6 years and above and with a body weight less than 20 kg should be treated with caution.

It is not always possible to precisely achieve the calculated dose with the commercially available capsule strengths of Zonisamide. In these cases, it is therefore recommended that the Zonisamide total dose should be rounded up or down to the nearest available dose that can be achieved with commercially available capsule strengths of Zonisamide (25 mg, 50 mg and 100 mg).

Withdrawal

When Zonisamide Waymade hard capsules treatment is to be discontinued, it should be withdrawn gradually (see section 4.4). In clinical studies of paediatric patients, down-titration was completed by dose reductions at weekly intervals in increments of about 2 mg/kg (i.e. in accordance with the schedule in Table 3).

Table 3. Paediatric population (aged 6 years and above) – recommended down-titration Schedule

Weight	Decrease at weekly intervals in increments of:
20 – 28 kg	25 to 50 mg / day*

29 – 41 kg	50 to 75 mg / day*
42 – 55 kg	100 mg / day*
>55 kg	100 mg / day*

Note:

* All doses are once daily.

Elderly

Caution should be exercised at initiation of treatment in elderly patients as there is limited information on the use of Zonisamide Waymade hard capsules in these patients. Prescribers should also take account of the safety profile of Zonisamide Waymade hard capsules (see section 4.8).

Patients with renal impairment

Caution must be exercised in treating patients with renal impairment, as there is limited information on use in such patients and a slower titration of Zonisamide Waymade hard capsules might be required. Since zonisamide and its metabolites are excreted renally, it should be discontinued in patients who develop acute renal failure or where a clinically significant sustained increase in serum creatinine is observed.

In subjects with renal impairment, renal clearance of single doses of zonisamide was positively correlated with creatinine clearance. The plasma AUC of zonisamide was increased by 35% in subjects with creatinine clearance < 20 ml/min.

Patients with hepatic impairment

Use in patients with hepatic impairment has not been studied. Therefore, use in patients with severe hepatic impairment is not recommended. Caution must be exercised in treating patients with mild to moderate hepatic impairment, and a slower titration of Zonisamide Waymade hard capsules may be required.

Method of administration

Zonisamide Waymade hard capsules are for oral use.

Effect of food

Zonisamide Waymade hard capsules may be taken with or without food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or to sulphonamides.

Zonisamide Waymade contains hydrogenated vegetable oil (from soybean). Patients must not take this medicinal product if they are allergic to peanut or soya.

4.4 Special warnings and precautions for use

Unexplained rash

Serious rashes occur in association with zonisamide therapy, including cases of Stevens-Johnson syndrome.

Consideration must be given to discontinuing Zonisamide Waymade hard capsules in patients who develop an otherwise unexplained rash. All patients who develop a rash while taking Zonisamide Waymade hard capsules must be closely supervised, with additional levels of caution applied to those patients receiving concomitant antiepileptic agents that may independently induce skin rashes.

Withdrawal seizures

In accordance with current clinical practice, discontinuation of Zonisamide Waymade hard capsules in patients with epilepsy must be accomplished by gradual dose reduction, to reduce the possibility of seizures on withdrawal. There are insufficient data for the withdrawal of concomitant antiepileptic medicines once seizure control with Zonisamide Waymade hard capsules has been achieved in the add-on situation, in order to reach monotherapy with Zonisamide Waymade hard capsules. Therefore, withdrawal of concomitant anti-epileptic medicinal products must be undertaken with caution.

Sulphonamide reactions

Zonisamide is a benzisoxazole derivative, which contains a sulphonamide group. Serious immune based adverse reactions that are associated with medicinal products containing a sulphonamide group include rash, allergic reaction and major haematological disturbances, including aplastic anaemia, which very rarely can be fatal.

Cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.

Acute myopia and secondary angle closure glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in adult and paediatric patients receiving zonisamide. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, and ocular hyperaemia (redness) and increased intraocular pressure. This syndrome may be associated with supraciliary effusion

resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms may occur within hours to weeks of initiating therapy. Treatment includes discontinuation of zonisamide, as rapidly as possible in the judgment of the treating physician, and appropriate measures to reduce intraocular pressure. Elevated intraocular pressure of any aetiology, if left untreated, can lead to serious sequelae including permanent vision loss. Caution should be used when treating patients with history of eye disorders with zonisamide.

Suicide ideation and behaviour

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

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

Kidney stones

Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Nephrolithiasis may lead to chronic kidney damage. Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during zonisamide treatment. In addition, patients taking other medications associated with nephrolithiasis may be at increased risk. Increasing fluid intake and urine output may help reduce the risk of stone formation, particularly in those with predisposing risk factors.

Metabolic acidosis

Hyperchloraemic, non-anion gap, metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with Zonisamide Waymade hard capsules treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of zonisamide on carbonic anhydrase. Such electrolyte imbalance has been observed with the use of Zonisamide Waymade hard capsules in placebo-controlled clinical trials and in the post-marketing period. Generally, zonisamide-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. The amounts by which bicarbonate is decreased are usually small – moderate (average decrease of approximately 3.5 mEq/l at daily doses of 300 mg in adults); rarely patients can experience more severe decreases. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or medicinal products) may be additive to the bicarbonate lowering effects of zonisamide.

The risk of zonisamide-induced metabolic acidosis appears to be more frequent and severe in younger patients. Appropriate evaluation and monitoring of serum bicarbonate levels

should be carried out in patients taking zonisamide who have underlying conditions which might increase the risk of acidosis, in patients who are at an increased risk of adverse consequences of metabolic acidosis and in patients with symptoms suggestive of metabolic acidosis. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing Zonisamide Waymade hard capsules (by gradual discontinuation or reduction of a therapeutic dose) as osteopenia may develop. If the decision is made to continue patients on Zonisamide Waymade hard capsules in the face of persistent acidosis, alkali treatment should be considered.

Metabolic acidosis has the potential to lead to hyperammonaemia, which has been reported with or without encephalopathy during zonisamide treatment. The risk for hyperammonaemia may be increased in patients concomitantly taking other medications that can cause hyperammonaemia (e.g. valproate), or who have an underlying urea cycle disorder or reduced hepatic mitochondrial activity. In patients who develop unexplained lethargy or changes in mental status during treatment with zonisamide, it is recommended to consider hyperammonaemia encephalopathy and to measure ammonia levels.

Zonisamide Waymade hard capsules should be used with caution in adult patients being treated concomitantly with carbonic anhydrase inhibitors such as topiramate or acetazolamide, as there are insufficient data to rule out a pharmacodynamic interaction (see also section 4.4 Paediatric population and section 4.5).

Heat stroke

Cases of decreased sweating and elevated body temperature have been reported mainly in paediatric patients (see section 4.4 Paediatric population for full warning). Caution should be used in adults when Zonisamide Waymade hard capsules are prescribed with other medicinal products that predispose patients to heat related disorders; these include carbonic anhydrase inhibitors and medicinal products with anticholinergic activity (see also section 4.4 Paediatric population)

Pancreatitis

In patients taking Zonisamide Waymade hard capsules who develop the clinical signs and symptoms of pancreatitis, it is recommended that pancreatic lipase and amylase levels are monitored. If pancreatitis is evident, in the absence of another obvious cause, it is recommended that discontinuation of Zonisamide Waymade hard capsules be considered and appropriate treatment initiated.

Rhabdomyolysis

In patients taking Zonisamide Waymade hard capsules, in whom severe muscle pain and/or weakness develop either in the presence or absence of a fever, it is recommended that markers of muscle damage be assessed, including serum creatine phosphokinase and aldolase levels. If elevated, in the absence of another obvious cause such as trauma or grand mal seizures, it is recommended that Zonisamide Waymade hard capsules discontinuation be considered and appropriate treatment initiated.

Women of child-bearing potential

Women of child-bearing potential must use effective contraception during treatment with Zonisamide Waymade hard capsules and for one month after discontinuation (see section 4.6). Zonisamide must not be used in women of child-bearing potential not using effective contraception unless clearly necessary and only if the potential benefit is considered to justify the risk to the foetus. Specialist advice should be given to women who are of child-bearing potential regarding the possible effects of Zonisamide Waymade on the foetus and those risks should be discussed with the patient in relation to the benefits before starting treatment. Women planning a pregnancy should meet with their specialists to reassess treatment with Zonisamide Waymade and to plan other therapeutic options. Physicians treating patients with Zonisamide Waymade hard capsules should ensure that patients are fully informed about the need to use appropriate effective contraception, and should use clinical judgement when assessing whether oral contraceptives (OCs), or the doses of the OC components, are adequate, based on the individual patient's clinical situation.

Body weight

Zonisamide may cause weight loss. A dietary supplement or increased food intake may be considered if the patient is losing weight or is underweight whilst on this medication. If substantial undesirable weight loss occurs, discontinuation of Zonisamide Waymade hard capsules should be considered. Weight loss is potentially more serious in children (see section 4.4. Paediatric population).

Paediatric population

The warnings and precautions mentioned above are also applicable to adolescent and paediatric patients. The warnings and precautions mentioned below are more relevant to paediatric and adolescent patients.

Heat stroke and dehydration

Preventing overheating and dehydration in children

Zonisamide Waymade hard capsules can cause children to sweat less and overheat and if the child is not treated this can lead to brain damage and death. Children are most at risk especially in hot weather.

When a child is taking Zonisamide Waymade hard capsules:

- The child should stay cool especially in hot weather
- The child must avoid heavy exercise especially when the weather is hot
- The child must drink plenty of cold water
- The child must not take any of these medicines:

carbonic anhydrase inhibitors (like topiramate and acetazolamide), and anticholinergic agents (like clomipramine, hydroxyzine, diphenhydramine, haloperidol, imipramine and oxybutynin).

IF ANY OF THE FOLLOWING OCCUR, THE CHILD NEEDS URGENT MEDICAL ATTENTION:

The skin feels very hot with little or no sweating, or the child becomes confused or has muscle cramps, or the child's heartbeat or breathing become rapid.

- Take the child to a cool, shaded place
- Keep the child's skin cool with water
- Give the child cold water to drink

Cases of decreased sweating and elevated body temperature have been reported mainly in paediatric patients. Heat stroke requiring hospital treatment was diagnosed in some cases. Heat stroke requiring hospital treatment and leading to death has been reported. Most reports occurred during periods of warm weather. Physicians should discuss with patients and their carers the potential seriousness of heat stroke, situations in which it might arise, as well as action to take in the event of any signs or symptoms. Patients or their carers must be warned to take care to maintain hydration and avoid exposure to excessive temperatures and strenuous physical exercise depending on the condition of the patient. Prescribers should draw the attention of paediatric patients and their parent/carers to the advice in the Packaging Leaflet on preventing heat stroke and overheating in children as provided. In the event of signs or symptoms of dehydration, oligohydrosis, or elevated body temperature, discontinuation of Zonisamide Waymade hard capsules should be considered.

Zonisamide Waymade hard capsules should not be used as co-medication in paediatric patients with other medicinal products that predispose patients to heat related disorders; these include carbonic anhydrase inhibitors and medicinal products with anticholinergic activity.

Body weight

Weight loss leading to deterioration of general condition and failure to take anti-epilepsy medication has been related to a fatal outcome (see section 4.8). Zonisamide Waymade hard capsules is not recommended for paediatric patients who are underweight (definition in accordance with the WHO age adjusted BMI categories) or have a decreased appetite.

The incidence of decreased body weight is consistent across age groups (see section 4.8); however, given the potential seriousness of weight loss in children, weight should be monitored in this population. A dietary supplement or increased food intake should be considered if the patient is failing to gain weight in accordance with growth charts, otherwise Zonisamide Waymade hard capsules should be discontinued.

There are limited data from clinical studies in patients with a body weight of less than 20 kg. Therefore, children aged 6 years and above with a body weight of less than 20 kg should be treated with caution. The long term effect of weight loss in the paediatric population on growth and development is unknown.

Metabolic acidosis

The risk of zonisamide-induced metabolic acidosis appears to be more frequent and severe in paediatric and adolescent patients. Appropriate evaluation and monitoring of serum bicarbonate levels should be carried out in this population (see section 4.4 - Metabolic acidosis for full warning; see section 4.8 for incidence of low bicarbonate). The long term effect of low bicarbonate levels on growth and development is unknown.

Zonisamide Waymade hard capsules should not be used as co-medication in paediatric patients with other carbonic anhydrase inhibitors such as topiramate and acetazolamide (see section 4.5).

Kidney stones

Kidney stones have occurred in paediatric patients (see section 4.4 Kidney stones for full warning). Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Nephrolithiasis may lead to chronic kidney damage. Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during zonisamide treatment.

Increasing fluid intake and urine output may help reduce the risk of stone formation, particularly in those with predisposing risk factors. Renal ultrasound should be performed at the discretion of the physician. In the event kidney stones are detected, Zonisamide Waymade hard capsules should be discontinued.

Hepatic dysfunction

Increased levels of hepatobiliary parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) and bilirubin have occurred in paediatric and adolescent patients, without any consistent pattern in the observations of values above the upper limit of normal. Nevertheless, if a hepatic event is suspected, liver function should be evaluated and discontinuation of Zonisamide Waymade hard capsules should be considered.

Cognition

Cognitive impairment in patients affected by epilepsy has been associated with the underlying pathology and/or the administration of anti-epileptic treatment. In a zonisamide placebo-controlled study conducted in paediatric and adolescent patients, the proportion of patients with impaired cognition was numerically greater in the zonisamide group compared with the placebo group.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Zonisamide Waymade hard capsules on cytochrome P450 enzymes

In vitro studies using human liver microsomes show no or little (<25%) inhibition of cytochrome P450 isozymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4 at zonisamide levels approximately twofold or greater than clinically relevant unbound serum concentrations. Therefore,

Zonisamide Waymade hard capsules are not expected to affect the pharmacokinetics of other medicinal products via cytochrome P450-mediated mechanisms, as demonstrated for carbamazepine, phenytoin, ethinylestradiol and desipramine *in vivo*.

Potential for Zonisamide Waymade hard capsules to affect other medicinal products

Anti-epileptic medicinal products

In epileptic patients, steady-state dosing with Zonisamide Waymade hard capsules resulted in no clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, or sodium valproate.

Oral contraceptives

In clinical studies in healthy subjects, steady-state dosing with Zonisamide did not affect serum concentrations of ethinylestradiol or norethisterone in a combined oral contraceptive.

Carbonic anhydrase inhibitors

Zonisamide Waymade hard capsules should be used with caution in adult patients treated concomitantly with carbonic anhydrase inhibitors such as topiramate and acetazolamide, as there are insufficient data to rule out a possible pharmacodynamic interaction (see section 4.4).

Zonisamide should not be used as co-medication in paediatric patients with other carbonic anhydrase inhibitors such as topiramate and acetazolamide (see section 4.4 Paediatric population).

P-gp substrate

An *in vitro* study shows that zonisamide is a weak inhibitor of P-gp (MDR1) with an IC₅₀ of 267 µmol/l and there is the theoretical potential for zonisamide to affect the pharmacokinetics of substances which are P-gp substrates. Caution is advised when starting or stopping zonisamide treatment or changing the zonisamide dose in patients who are also receiving medicinal products which are P-gp substrates (e.g. digoxin, quinidine).

Potential medicinal product interactions affecting Zonisamide Waymade hard capsules

In clinical studies co-administration of lamotrigine had no apparent effect on zonisamide pharmacokinetics. The combination of Zonisamide with other medicinal products that may lead to urolithiasis may enhance the risk of developing kidney stones; therefore the concomitant administration of such medicinal products should be avoided.

Zonisamide is metabolised partly by CYP3A4 (reductive cleavage), and also by N-acetyltransferases and conjugation with glucuronic acid; therefore, substances that can induce or inhibit these enzymes may affect the pharmacokinetics of zonisamide:

- Enzyme induction: Exposure to zonisamide is lower in epileptic patients receiving CYP3A4-inducing agents such as phenytoin, carbamazepine, and phenobarbitone. These effects are unlikely to be of clinical significance when Zonisamide is added to existing therapy; however, changes in zonisamide concentrations may occur if concomitant CYP3A4-inducing anti-epileptic or other medicinal products are withdrawn, dose adjusted or introduced, an adjustment of the Zonisamide Waymade hard capsules dose may be required. Rifampicin is a potent CYP3A4 inducer. If co-administration is necessary, the patient should be closely monitored and the dose of Zonisamide Waymade hard capsules and other CYP3A4 substrates adjusted as needed.

- CYP3A4 inhibition: Based upon clinical data, known specific and non-specific CYP3A4 inhibitors appear to have no clinically relevant effect on zonisamide pharmacokinetic exposure parameters. Steady-state dosing of either ketoconazole (400 mg/day) or cimetidine (1200 mg/day) had no clinically relevant effects on the single-dose pharmacokinetics of zonisamide given to healthy subjects. Therefore, modification of Zonisamide dosing should not be necessary when co-administered with known CYP3A4 inhibitors.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Women of child-bearing potential must use effective contraception during treatment with Zonisamide Waymade hard capsules, and for one month after discontinuation.

Zonisamide Waymade hard capsules must not be used in women of child-bearing potential not using effective contraception unless clearly necessary and only if the potential benefit is considered to justify the risk to the foetus. Specialist medical advice should be given to women treated with zonisamide who are of child-bearing potential. Women planning a pregnancy should meet with their specialists to reassess treatment with zonisamide and to consider other therapeutic options.

As with all antiepileptic medicines, sudden discontinuation of zonisamide should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. The risk of birth defect is increased by factor 2 to 3 in the offspring of mothers treated with an epileptic medicinal product. The most frequently reported are cleft lip, cardiovascular malformations and neural tube defect. Multiple antiepileptic medicinal product therapy may be associated with a higher risk of congenital malformations than monotherapy.

Pregnancy

There are limited data from the use of Zonisamide Waymade hard capsules in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Data from a registry study suggest an increase in the proportion of babies born at a low birth weight (LBW), pre-term or small for gestational age (SGA). These increases are from about 5% to 8% for LBW, from about 8% to 10% for pre-term birth and from about 7% to 12% for SGA, all compared to mothers treated with lamotrigine monotherapy.

Zonisamide Waymade hard capsules must not be used during pregnancy unless clearly necessary and only if the potential benefit is considered to justify the risk to the foetus. If Zonisamide Waymade hard capsules are prescribed during pregnancy, patients should be

informed of the potential harm to the foetus and use of the minimal effective dose is advised along with careful monitoring.

Breast-feeding

Zonisamide is excreted in human milk; the concentration in breast milk is similar to maternal plasma. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Zonisamide Waymade hard capsules therapy. Due to the long retention time of zonisamide in the body, breast-feeding must not be resumed until one month after Zonisamide Waymade hard capsules therapy is completed.

Fertility

There are no clinical data available on the effects of zonisamide on human fertility. Studies in animals have shown changes in fertility parameters (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, given that some patients may experience drowsiness or difficulty with concentration, particularly early in treatment or after a dose increase, patients must be advised to exercise caution during activities requiring a high degree of alertness, e.g., driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

Zonisamide has been administered to over 1,200 patients in clinical studies, more than 400 of whom received zonisamide for at least 1 year. In addition there has been extensive post-marketing experience with zonisamide in Japan since 1989 and in the USA since 2000.

It should be noted that zonisamide is a benzisoxazole derivative, which contains a sulphonamide group. Serious immune based adverse reactions that are associated with medicinal products containing a sulphonamide group include rash, allergic reaction and major haematological disturbances including aplastic anaemia, which very rarely can be fatal (see section 4.4).

The most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia. The most common adverse reactions in a randomised, controlled monotherapy trial comparing zonisamide with carbamazepine prolonged release were decreased bicarbonate, decreased appetite, and decreased weight. The incidence of markedly abnormally low serum bicarbonate (a decrease to less than 17 mEq/l and by more than 5 mEq/l) was 3.8%. The incidence of marked decreases in weight of 20% or more was 0.7%.

Tabulated list of adverse reactions

Adverse reactions associated with zonisamide obtained from clinical studies and post-marketing surveillance are tabulated below. The frequencies are arranged according to the following scheme:

Very common	$\geq 1/10$
Common	$\geq 1/100$ to $< 1/10$
Uncommon	$\geq 1/1,000$ to $< 1/100$
Rare	$\geq 1/10,000$ to $< 1/1,000$
Very rare	$< 1/10,000$
Not known	cannot be estimated from the available data

Table 4. Adverse reactions associated with Zonisamide obtained from adjunctive use clinical studies and post-marketing surveillance

System Organ Class (MedDRA terminology)	Very Common	Common	Uncommon	Very Rare
Infections and infestation			Pneumonia Urinary tract infection	
Blood and lymphatic system disorders		Ecchymosis		Agranulocytosis Aplastic anaemia Leucocytosis Leucopenia Lymphadenopathy Pancytopenia, Thrombocytopenia

Immune system disorders		Hypersensitivity		Drug-induced hypersensitivity syndrome Drug rash with eosinophilia and systemic symptoms
Metabolism and nutrition disorders	Anorexia		Hypokalaemia	Metabolic acidosis Renal tubular acidosis
Psychiatric Disorders	Agitation Irritability Confusional state Depression	Affect lability Anxiety Insomnia Psychotic disorder	Anger Aggression Suicidal ideation Suicide attempt	Hallucination
Nervous system disorders	Ataxia Dizziness Memory impairment Somnolence	Bradypnea Disturbance in attention Nystagmus Paraesthesia Speech disorder Tremor	Convulsion	Amnesia Coma Grand mal seizure Myasthenic syndrome Neuroleptic malignant syndrome Status epilepticus
Eye disorders	Diplopia			Angle closure glaucoma Eye pain Myopia Vision blurred Visual acuity reduced
Respiratory, thoracic and mediastinal disorders				Dyspnoea Pneumonia aspiration Respiratory disorder Hypersensitivity-type Pneumonitis

Gastrointestinal disorders		Abdominal pain Constipation Diarrhoea Dyspepsia Nausea	Vomiting	Pancreatitis
Hepatobiliary disorders			Cholecystitis Cholelithiasis	Hepato cellular damage
Skin and subcutaneous tissue disorders		Rash Pruritus Alopecia		Anhidrosis Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders				Rhabdomyolysis
Renal and urinary disorders		Nephrolithiasis	Calculus urinary	Hydronephrosis Renal failure Urine abnormality
General disorders and administration site conditions		Fatigue Influenza-like illness Pyrexia Oedema peripheral		
Investigations	Decreased bicarbonate	Weight decreased		Blood creatine phosphokinase increased Blood creatinine increased Blood urea increased Liver function tests abnormal

Injury, poisoning and procedural complications				Heat stroke
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In addition there have been isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP) receiving zonisamide.

Table 5. Adverse reactions in a randomised, controlled monotherapy trial comparing zonisamide with carbamazepine prolonged release

System Organ Class (MedDRA terminology†)	Very Common	Common	Uncommon
Infections and infestation			Urinary tract infection Pneumonia
Blood and lymphatic disorders			Leukopenia Thrombocytopenia
Metabolism and nutrition disorders		Decreased appetite	Hypokalaemia
Psychiatric Disorders		Agitation Depression Insomnia Mood swings Anxiety	Confusional state Acute psychosis Aggression Suicidal ideation Hallucination

Nervous system disorders		Ataxia Dizziness Memory impairment Somnolence Bradypnea Disturbance in attention Paraesthesia	Nystagmus Speech disorder Tremor Convulsion
Eye disorders		Diplopia	
Respiratory, thoracic and mediastinal disorders			Respiratory disorder
Gastrointestinal disorders		Constipation Diarrhoea Dyspepsia Nausea Vomiting	Abdominal pain
Hepatobiliary disorders			Cholecystitis acute
Skin and subcutaneous tissue disorders		Rash	Pruritus Ecchymosis
General disorders and administration site conditions		Fatigue Pyrexia Irritability	
Investigations	Decreased bicarbonate	Weight decreased Blood creatinine phosphokinase increased Alanine aminotransferase increased Aspartate aminotransferase increased	Urine analysis abnormal

Additional information on special populations:

Elderly

A pooled analysis of safety data on 95 elderly subjects has shown a relatively higher reporting frequency of oedema peripheral and pruritus compared to the adult population.

Review of post-marketing data suggests that patients aged 65 years or older report a higher frequency than the general population of the following events: Stevens-Johnson syndrome (SJS) and Drug Induced Hypersensitivity syndrome (DIHS).

Paediatric population

The adverse event profile of zonisamide in paediatric patients aged 6 to 17 years in placebo-controlled clinical studies was consistent with that of adults. Among 465 subjects in the paediatric safety database (including a further 67 subjects from the extension phase of the controlled clinical trial) there were 7 deaths (1.5%; 14.6/1000 person-years): 2 cases of status epilepticus, of which one was related to severe weight loss (10% within 3 months) in an underweight subject and subsequent failure to take medication; 1 case of head injury/haematoma, and 4 deaths in subjects with pre-existing functional neurological deficits for various causes (2 cases of pneumonia-induced sepsis/organ failure, 1 SUDEP and 1 head injury). A total of 70.4% of paediatric subjects who received ZNS in the controlled study or its open label extension had at least one treatment-emergent bicarbonate measurement below 22 mmol/L. The duration of low bicarbonate measurements was also long (median 188 days).

A pooled analysis of safety data on 420 paediatric subjects (183 subjects aged 6 to 11 years, and 237 subjects aged 12 to 16 years with a mean duration of exposure of approximately 12 months) has shown a relatively higher reporting frequency of pneumonia, dehydration, decreased sweating, abnormal liver function tests, otitis media, pharyngitis, sinusitis and upper respiratory tract infection, cough, epistaxis and rhinitis, abdominal pain, vomiting, rash and eczema, and fever compared to the adult population (particularly in subjects aged below 12 years) and, at a low incidence, amnesia, creatinine increased, lymphadenopathy, and thrombocytopenia. The incidence of a decrease in body weight of 10% or more was 10.7% (see section 4.4). In some cases of weight decrease there was a delay in transition to the next Tanner stage and in bone maturation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There have been cases of accidental and intentional overdose in adult and paediatric patients. In some cases, the overdoses were asymptomatic, particularly where emesis or lavage was prompt. In other cases, the overdose was followed by symptoms such as somnolence, nausea, gastritis, nystagmus, myoclonus, coma, bradycardia, reduced renal function, hypotension and respiratory depression. A very high plasma concentration of 100.1 µg/ml zonisamide was recorded approximately 31 hours after a patient took an overdose of zonisamide and clonazepam; the patient became comatose and had respiratory depression, but recovered consciousness five days later and had no sequelae.

Treatment

No specific antidotes for Zonisamide Waymade hard capsules overdose are available. Following a suspected recent overdose, emptying the stomach by gastric lavage or by induction of emesis may be indicated with the usual precautions to protect the airway. General supportive care is indicated, including frequent monitoring of vital signs and close observation. Zonisamide has a long elimination half-life so its effects may be persistent. Although not formally studied for the treatment of overdose, haemodialysis reduced plasma concentrations of zonisamide in a patient with reduced renal function, and may be considered as treatment of overdose if clinically indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, other antiepileptics, ATC code: N03AX15
Zonisamide is a benzisoxazole derivative. It is an anti-epileptic medicine with weak carbonic anhydrase activity *in-vitro*. It is chemically unrelated to other anti-epileptic agents.

Mechanism of action

The mechanism of action of zonisamide is not fully elucidated, but it appears to act on voltage-sensitive sodium and calcium channels, thereby disrupting synchronised neuronal firing, reducing the spread of seizure discharges and disrupting subsequent epileptic activity. Zonisamide also has a modulatory effect on GABA-mediated neuronal inhibition.

Pharmacodynamic effects

The anticonvulsant activity of zonisamide has been evaluated in a variety of models, in several species with induced or innate seizures, and zonisamide appears to act as a broad-spectrum anti-epileptic in these models. Zonisamide prevents maximal electroshock seizures and restricts seizure spread, including the propagation of seizures from cortex to sub-cortical structures and suppresses epileptogenic focus activity. Unlike phenytoin and carbamazepine however, zonisamide acts preferentially on seizures originating in the cortex.

Clinical efficacy and safety

Monotherapy in partial seizures, with or without secondary generalisation

Efficacy of zonisamide as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine prolonged release (PR) in 583 adult subjects with newly diagnosed partial seizures with or without secondary generalised tonic-clonic seizures. Subjects were randomised to carbamazepine and zonisamide received treatment for a duration of up to 24 months depending on response. Subjects were titrated to the initial target dose of 600 mg carbamazepine or 300 mg of zonisamide. Subjects who experienced a seizure were titrated to the next target dose i.e. 800 mg carbamazepine or 400 mg of zonisamide. Subjects who experienced a further seizure were titrated to the maximal target dose of 1200 mg carbamazepine or 500 mg zonisamide. Subjects who were seizure-free for 26 weeks at a target dose level continued on this dose for another 26 weeks. Main outcomes of this study are presented in this table:

Table 6. Efficacy results for Monotherapy Study 310

	Zonisamide	Carbamazepine		
n (ITT population)	281	300		
Six months seizure freedom			Diff	CI _{95%}
PP-population*	79.4%	83.7%	-4.5%	-12.2% ; 3.1%
ITT-population	69.4%	74.7%	-6.1%	-13.6% ; 1.4%
≤4 seizures during 3 month baseline period	71.7%	75.7%	-4.0%	-11.7% ; 3.7%
> 4 seizures during 3 month baseline period	52.9%	68.9%	-15.9%	-37.5% ; 5.6%
Twelve months seizure freedom				
PP-population	67.6%	74.7%	-7.9%	- 17.2% ; 1.5%
ITT-population	55.9%	62.3%	-7.7%	- 16.1% ; 0.7%
≤ 4 seizures during 3 month baseline period	57.4%	64.7%	-7.2%	-15.7% ; 1.3%
> 4 seizures during 3 month baseline period	44.1%	48.9%	-4.8%	-26.9% ; 17.4%

Seizure Sub-type (6 month seizure freedom-PP population)				
All partial	76.4%	86.0%	-9.6%	-19.2% ; 0.0%
Simple partial	72.3%	75.0%	-2.7%	-20.0% ; 14.7%
Complex partial	76.9%	93.0%	-16.1%	-26.3% ; -5.9%
All generalized Tonic-Clonic	78.9%	81.6%	-2.8%	-11.5% ; 6.0%
Secondary Tonic-Clonic	77.4%	80.0%	-2.6%	-12.4% ; 7.1%
Generalized Tonic-Clonic	85.7%	92.0%	-6.3%	-23.1% ; 10.5%

PP = Per Protocol Population; ITT = Intent To Treat Population

*Primary endpoint

Adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation in adults

In adults, efficacy has been demonstrated with zonisamide in 4 double-blind, placebo-controlled studies of periods of up to 24 weeks with either once or twice daily dosing. These studies show that the median reduction in partial seizure frequency is related to zonisamide dose with sustained efficacy at doses of 300-500 mg per day.

Paediatric population

Adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adolescent and paediatric patients (aged 6 years and above)

In paediatric patients (aged 6 years and above), efficacy has been demonstrated with zonisamide in a double-blind, placebo-controlled study, which included 207 subjects and had a treatment duration of up to 24 weeks. A 50% or greater reduction from baseline in seizure frequency during the 12-week stable dose period was seen in 50% of the zonisamide-treated subjects and 31% of the patients on placebo.

Specific safety issues that were encountered in the paediatric studies were: decreased appetite and weight loss, decreased bicarbonate levels, increased risk of kidney stones and dehydration. All these effects and specifically weight loss may have deleterious implications for growth and development, and may lead to general deterioration of health. Altogether, data on effects on long-term growth and development are limited.

5.2 Pharmacokinetic properties

Absorption

Zonisamide is almost completely absorbed after oral administration, generally reaching peak serum or plasma concentrations within 2 to 5 hours of dosing. The first-pass metabolism is believed to be negligible. Absolute bioavailability is estimated to be approximately 100%. Oral bioavailability is not affected by food, although peak plasma and serum concentrations may be delayed.

Zonisamide AUC and C_{max} values increased almost linearly after single dose over the dose range of 100-800 mg and after multiple doses over the dose range of 100-400 mg once daily. The increase at steady state was slightly more than expected on the basis of dose, probably due to the saturable binding of zonisamide to erythrocytes. Steady state was achieved within 13 days. Slightly greater than expected accumulation occurs relative to single dosing.

Distribution

Zonisamide is 40 - 50 % bound to human plasma proteins, with *in vitro* studies showing that this is unaffected by the presence of various antiepileptic medicinal products (i.e., phenytoin, phenobarbitone, carbamazepine, and sodium valproate). The apparent volume of distribution is about 1.1 – 1.7 l/kg in adults indicating that zonisamide is extensively distributed to tissues. Erythrocyte/plasma ratios are about 15 at low concentrations and about 3 at higher concentrations.

Biotransformation

Zonisamide is metabolised primarily through reductive cleavage of the benzisoxazole ring of the parent drug by CYP3A4 to form 2-sulphamoylacetylphenol (SMAP) and also by N-acetylation. Parent drug and SMAP can additionally be glucuronidated. The metabolites, which could not be detected in plasma, are devoid of anticonvulsant activity. There is no evidence that zonisamide induces its own metabolism.

Elimination

Apparent clearance of zonisamide at steady-state after oral administration is about 0.70 l/h and the terminal elimination half-life is about 60 hours in the absence of CYP3A4 inducers. The elimination half-life was independent of dose and not affected by repeat administration. Fluctuation in serum or plasma concentrations over a dosing interval is low (< 30 %). The main route of excretion of zonisamide metabolites and unchanged drug is via the urine. Renal clearance of unchanged zonisamide is relatively low (approximately 3.5 ml/min); about 15 - 30 % of the dose is eliminated unchanged.

Linearity/non-linearity

Zonisamide exposure increases with time until steady state is achieved by approximately 8 weeks. When comparing the same dose level, subjects of higher total body weight appear to have lower steady-state serum concentrations, but this effect appears to be relatively modest. Age (≥ 12 years) and gender, after adjustment for body weight effects, have no apparent effect on zonisamide exposure in epileptic patients during steady-state dosing. There is no need for dose adjustment with any of the AEDs including CYP3A4 inducers.

Pharmacokinetic/pharmacodynamic relationship

Zonisamide lowers the 28-day average seizure frequency and the decrease is proportional (log-linear) to zonisamide average concentration.

Special patient groups

In subjects with renal impairment, renal clearance of single doses of zonisamide was positively correlated with creatinine clearance. The plasma AUC of zonisamide was increased by 35% in subjects with creatinine clearance <20 ml/min (see also section 4.2.).

Patients with an impaired liver function: The pharmacokinetics of zonisamide in patients with impaired liver function have not been adequately studied.

Elderly: No clinically significant differences were observed in the pharmacokinetics between young (aged 21-40 years) and elderly (65-75 years).

Children and adolescents (5-18 years): Limited data indicate that pharmacokinetics in children and adolescents dosed to steady state at 1, 7 or 12 mg/kg daily, in divided doses, are similar to those observed in adults, after adjustment for bodyweight.

5.3 Preclinical safety data

Findings not observed in clinical studies, but seen in the dog at exposure levels similar to clinical use, were liver changes (enlargement, dark-brown discolouration, mild hepatocyte enlargement with concentric lamellar bodies in the cytoplasm and cytoplasmic vacuolation) associated with increased metabolism.

Zonisamide was not genotoxic and has no carcinogenic potential.

Zonisamide was embryotoxic and teratogenic (reduced pup weight, increase in cardiac and major blood vessel defects, delayed ossification) in mice, rats and dogs and induced maternal toxicity at high doses. In monkeys zonisamide acted as an abortifacient at all doses tested and given the embryoletality a teratogenic potential in monkeys cannot be ruled out. Zonisamide also causes a reduction in food consumption, reduced maternal and fetal bodyweight gain and a reduction in growth parameters in the fetus (small for gestational weight). The plasma concentrations associated with the embryotoxicity was within the therapeutic range.

In a repeated-dose oral toxicity study in juvenile rats, at exposure levels similar to those observed in paediatric patients at the maximum recommended dose, decreases in body weight and changes in renal histopathology and clinical pathology parameters and behavioural changes were observed. Changes in renal histopathology and clinical pathology parameters were considered to be related to carbonic anhydrase inhibition by zonisamide. The effects at this dose level were reversible during the recovery period. At a higher dose level (2-3-fold systemic exposure compared to therapeutic exposure) renal histopathological effects were more severe and only partially reversible. Most adverse effects observed in the juvenile rats were similar to those seen in the repeated-dose toxicity studies of zonisamide in adult rats, but renal tubular hyaline droplets and transitional hyperplasia were observed in the juvenile study only. At this higher dose level, juvenile rats showed a decrease in growth, learning, and developmental parameters. These effects were considered likely related to the

decreased body weight and exaggerated pharmacologic effects of zonisamide at the maximum tolerated dose.

In rats, decreased numbers of corpora lutea and implantation sites were observed at exposure levels equivalent to the maximum therapeutic dose in humans; irregular oestrus cycles and a decreased number of live foetuses were observed at exposure levels three times higher.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Microcrystalline cellulose

Hydrogenated vegetable oil (from soybean)

Sodium laurilsulfate

Silica colloidal anhydrous

Capsule shell (size "1")

Gelatin

Titanium dioxide (E171)

Allura red (E129)

Sunset yellow (E110)

Black Ink (Black iron oxide E172, shellac, propylene glycol, strong ammonia solution (pH adjustment) and potassium hydroxide (pH adjustment))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PVDC/aluminium blisters, packs of 56 hard capsules.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Waymade PLC trading as Sovereign Medical
Sovereign House
Miles Gray Road
Basildon
Essex
SS14 3FR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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